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Vitamin supplementation for preventing miscarriage (Review)

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[Intervention Review]

Vitamin supplementation for preventing miscarriage

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ABSTRACT

Background

Miscarriage is a common complication of pregnancy that can be caused by a wide range of factors. Poor dietary intake of vitamins has been associated with an increased risk of miscarriage, therefore supplementing women with vitamins either prior to or in early pregnancy may help prevent miscarriage.

Objectives

The objectives of this review were to determine the effectiveness and safety of any vitamin supplementation, on the risk of spontaneous miscarriage.

Search methods

We searched the Cochrane Pregnancy and Childbirth Group Trials Register (6 November 2015) and reference lists of retrieved studies.

Selection criteria

All randomised and quasi-randomised trials comparing supplementation during pregnancy with one or more vitamins with either placebo, other vitamins, no vitamins or other interventions. We have included supplementation that started prior to conception, periconceptionally or in early pregnancy (less than 20 weeks' gestation).

Data collection and analysis

Three review authors independently assessed trials for inclusion, extracted data and assessed trial quality. We assessed the quality of the evidence using the GRADE approach. The quality of evidence is included for numerical results of outcomes included in the 'Summary of findings' tables.

Main results

We included a total of 40 trials (involving 276,820 women and 278,413 pregnancies) assessing supplementation with any vitamin(s) starting prior to 20 weeks' gestation and reporting at least one primary outcome that was eligible for the review. Eight trials were cluster-randomised and contributed data for 217,726 women and 219,267 pregnancies in total.

Approximately half of the included trials were assessed to have a low risk of bias for both random sequence generation and adequate concealment of participants to treatment and control groups.

Vitamin C supplementation

There was no difference in the risk of total fetal loss (risk ratio (RR) 1.14, 95% confidence interval (CI) 0.92 to 1.40, seven trials, 18,949 women; *high-quality evidence*); early or late miscarriage (RR 0.90, 95% CI 0.65 to 1.26, four trials, 13,346 women; *moderate-quality evidence*); stillbirth (RR 1.31, 95% CI 0.97 to 1.76, seven trials, 21,442 women; *moderate-quality evidence*) or adverse effects of vitamin supplementation (RR 1.16, 95% CI 0.39 to 3.41, one trial, 739 women; *moderate-quality evidence*) between women receiving vitamin C with vitamin E compared with placebo or no vitamin C groups. No clear differences were seen in the risk of total fetal loss or miscarriage between women receiving any other combination of vitamin C compared with placebo or no vitamin C groups.

Vitamin A supplementation

No difference was found in the risk of total fetal loss (RR 1.01, 95% CI 0.61 to 1.66, three trials, 1640 women; *low-quality evidence*); early or late miscarriage (RR 0.86, 95% CI 0.46 to 1.62, two trials, 1397 women; *low-quality evidence*) or stillbirth (RR 1.29, 95% CI 0.57 to 2.91, three trials, 1640 women; *low-quality evidence*) between women receiving vitamin A plus iron and folate compared with placebo or no vitamin A groups. There was no evidence of differences in the risk of total fetal loss or miscarriage between women receiving any other combination of vitamin A compared with placebo or no vitamin A groups.

Multivitamin supplementation

There was evidence of a decrease in the risk for stillbirth among women receiving multivitamins plus iron and folic acid compared iron and folate only groups (RR 0.92, 95% CI 0.85 to 0.99, 10 trials, 79,851 women; *high-quality evidence*). Although total fetal loss was lower in women who were given multivitamins without folic acid (RR 0.49, 95% CI 0.34 to 0.70, one trial, 907 women); and multivitamins with or without vitamin A (RR 0.60, 95% CI 0.39 to 0.92, one trial, 1074 women), these findings included one trial each with small numbers of women involved. Also, they include studies where the comparison groups included women receiving either vitamin A or placebo, and thus require caution in interpretation.

We found no difference in the risk of total fetal loss (RR 0.96, 95% CI 0.93 to 1.00, 10 trials, 94,948 women; *high-quality evidence*) or early or late miscarriage (RR 0.98, 95% CI 0.94 to 1.03, 10 trials, 94,948 women; *moderate-quality evidence*) between women receiving multivitamins plus iron and folic acid compared with iron and folate only groups.

There was no evidence of differences in the risk of total fetal loss or miscarriage between women receiving any other combination of multivitamins compared with placebo, folic acid or vitamin A groups.

Folic acid supplementation

There was no evidence of any difference in the risk of total fetal loss, early or late miscarriage, stillbirth or congenital malformations between women supplemented with folic acid with or without multivitamins and/or iron compared with no folic acid groups.

Antioxidant vitamins supplementation

There was no evidence of differences in early or late miscarriage between women given antioxidant compared with the low antioxidant group (RR 1.12, 95% CI 0.24 to 5.29, one trial, 110 women).

Authors' conclusions

Taking any vitamin supplements prior to pregnancy or in early pregnancy does not prevent women experiencing miscarriage. However, evidence showed that women receiving multivitamins plus iron and folic acid had reduced risk for stillbirth. There is insufficient evidence to examine the effects of different combinations of vitamins on miscarriage and miscarriage-related outcomes.

PLAIN LANGUAGE SUMMARY

Vitamin supplementation for preventing miscarriage

What is the issue?

Miscarriage occurs frequently among pregnant women but it is often difficult to know the factors responsible. Poor diet, without enough vitamins, has been associated with an increased risk of women losing their baby in early pregnancy. Does vitamin supplementation taken by women before pregnancy and during pregnancy decrease the risk of spontaneous miscarriage? Does supplementation improve maternal, birth and infant outcomes, and are there any side effects?

Why is this important?

Vitamin supplementation is commonly recommended for pregnant women and women planning to conceive. Considering the widespread use of vitamin supplementation before and during pregnancy, it is important to study the relation between vitamin supplementation and early pregnancy outcomes, particularly since the causes of miscarriage are unknown and the nutritional status of a mother can affect her baby's development.

What evidence did we find?

This review included 40 randomised controlled trials involving 276,820 women and 278,413 pregnancies. Supplementing women with any vitamins does not reduce the number of women who have miscarriages. However, the risk for stillbirth was reduced among women receiving multivitamins plus iron and folic acid compared with iron and folate only groups. Although total fetal loss was lower in women who were given multivitamins without folic acid and multivitamins with or without vitamin A, these findings included one trial each with small numbers of women involved. Also, they include studies where the comparison groups included women receiving either vitamin A or placebo, and thus require caution in interpretation.

What does this mean?

Taking vitamin supplements before pregnancy or in early pregnancy may be beneficial; but this review did not show sufficient evidence that taking vitamin supplements prevents miscarriage.

Summary of findings for the main comparison. Vitamin C and vitamin E versus placebo for preventing miscarriage

Vitamin C plus vitamin E versus control for preventing miscarriage

Population: pregnant women
Setting: Australia, Brazil, Canada, Scotland, UK, USA
Intervention: vitamin C and vitamin E
Comparison: placebo

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with placebo	Risk with Vitamin C plus vitamin E				
Total fetal loss	Study population		RR 1.14 (0.92 to 1.40)	18,949 (7 RCTs)	⊕⊕⊕⊕ HIGH [1]	
	17 per 1000	20 per 1000 (16 to 24)				
	Moderate					
	14 per 1000	16 per 1000 (13 to 20)				
Early or late miscarriage	Study population		RR 0.90 (0.65 to 1.26)	13,346 (4 RCTs)	⊕⊕⊕⊖ MODERATE [2]	
	9 per 1000	9 per 1000 (7 to 12)				
	Moderate					
	8 per 1000	8 per 1000 (6 to 11)				
Stillbirth	Study population		RR 1.31 (0.97 to 1.76)	21,442 (7 RCTs)	⊕⊕⊕⊖ MODERATE [2]	
	8 per 1000	10 per 1000 (7 to 13)				
	Moderate					
	7 per 1000	9 per 1000				

		(7 to 12)			
Any adverse effects of vitamin supplementation sufficient to stop supplementation	Study population		RR 1.16 (0.39 to 3.41)	739 (1 RCT)	⊕⊕⊕⊖ MODERATE [2 3]
	16 per 1000	19 per 1000 (6 to 56)			

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio

GRADE Working Group grades of evidence
High quality: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

[1] Not effective but 95% CI is narrow and precise.
[2] Non significant with wide 95% CI.
[3] Small sample size.

Summary of findings 2. Vitamin A plus iron plus folate versus iron plus folate for preventing miscarriage

Vitamin A plus iron plus folate versus iron plus folate for preventing miscarriage

Population: pregnant women
Settings: Indonesia, Malawi
Intervention: vitamin A plus iron plus folate
Comparison: iron plus folate

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with placebo	Risk with Vitamin A				
Total fetal loss (including miscarriages or combined miscarriages and stillbirths) - Vitamin A + iron + folate versus iron + folate	Study population		RR 1.01 (0.61 to 1.66)	1640 (3 RCTs)	⊕⊕⊖⊖ LOW [1 2]	
	37 per 1000	37 per 1000 (22 to 61)				
	Moderate					

	59 per 1,000	60 per 1,000 (36 to 98)				
Early or late miscarriage - Vitamin A + iron + folate versus iron + folate	Study population		RR 0.86 (0.46 to 1.62)	1397 (2 RCTs)	⊕⊕⊖⊖ LOW [1] [2]	
	31 per 1000	26 per 1000 (14 to 50)				
	Moderate					
	50 per 1,000	43 per 1,000 (23 to 80)				
Stillbirth - Vitamin A + iron + folate versus iron + folate	Study population		RR 1.29 (0.57 to 2.91)	1640 (3 RCTs)	⊕⊕⊖⊖ LOW [1] [2]	
	13 per 1000	16 per 1000 (7 to 37)				
	Moderate					
	21 per 1,000	27 per 1,000 (12 to 61)				
Any adverse effects			See comments.			No studies reported this outcome.

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).

__CI:__ Confidence interval; __RR:__ Risk ratio

GRADE Working Group grades of evidence
High quality: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

[1] High and unclear risk of attrition bias.
[2] Wide 95% CI.

Summary of findings 3. Multivitamin plus iron plus folate versus iron plus folate for preventing miscarriage

Multivitamin plus iron plus folate versus iron plus folate for preventing miscarriage

Population: pregnant women
Settings: Bangladesh, Barkino Faso, Indonesia, Nepal, Niger, Pakistan, Tanzania
Intervention: vitamin A plus iron plus folate
Comparison: iron plus folate

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with placebo	Risk with Multivitamin				
Total fetal loss (including miscarriages or combined miscarriages and stillbirths) - Multivitamins + iron + folic acid versus iron + folic acid	Study population		RR 0.96 (0.93 to 1.00)	94,948 (10 RCTs)	⊕⊕⊕⊕ HIGH	
	136 per 1000	130 per 1000 (126 to 136)				
	Moderate					
	218 per 1,000	209 per 1,000 (202 to 218)				
Early or late miscarriage - Multivitamin + iron + folic acid versus iron + folic acid	Study population		RR 0.98 (0.94 to 1.03)	94948 (10 RCTs)	⊕⊕⊕⊖ MODERATE [1,2]	
	84 per 1000	83 per 1000 (79 to 87)				
	Moderate					
	134 per 1,000	132 per 1,000 (126 to 138)				
Stillbirth - Multivitamin + iron + folic acid versus iron + folic acid	Study population		RR 0.92 (0.85 to 0.99)	79,851 (10 RCTs)	⊕⊕⊕⊕ HIGH	
	29 per 1000	26 per 1000 (24 to 28)				
	Moderate					
	46 per 1,000	43 per 1,000				

	(39 to 46)		
Any adverse effects		See comments	No studies reported this outcome

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).
CI: Confidence interval; **RR:** Risk ratio

GRADE Working Group grades of evidence
High quality: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

[1] Publication bias detected by funnel plot.
[2] Wide confidence interval crossing the line of no effect.

BACKGROUND

Description of the condition

Miscarriage can be caused by a wide range of factors, and determining the aetiology is often difficult given the variety of underlying mechanisms potentially responsible. Consideration of the timing of the miscarriage is also important, as diverse causes of miscarriage manifest at different periods of gestation. The most common causes include abnormal chromosomal rearrangements, endocrinological disorders and uterine abnormalities (Garrido-Gimenez 2015). Early miscarriages are mostly associated with chromosomal abnormalities, defective placental development and maternal disease conditions; while late miscarriages are more likely due to structural problems of the uterus and/or cervix such as cervical incompetence. Women experiencing recurrent miscarriage often have an underlying medical condition such as autoimmune disease, i.e. systemic lupus erythematosus and antiphospholipid syndrome, or other blood clotting disorders such as hyperhomocysteinaemia (high levels of homocysteine in the blood) or another thrombophilia (Preston 1996). Other risk factors for miscarriage include higher maternal age at conception, multiple pregnancies and a history of previous miscarriage (Baba 2011; García-Enguídanos 2002; Hure 2012). Behavioural factors including alcohol consumption (Maconochie 2007), smoking (Baba 2011; Hure 2012), use of illicit drugs (García-Enguídanos 2002), and exposure to non-steroidal anti-inflammatory drugs (NSAIDs) around the time of conception are also suggested causes of miscarriage (Li 2003; Nielsen 2001). While several factors may promote miscarriage, for a great proportion of women, no cause can be found.

In clinical practice, surgical and non-surgical interventions are used in the management of miscarriage. Bed rest, commonly prescribed for preventing miscarriage, is lacking proven benefit (Aleman 2005). Similarly, there is currently insufficient evidence on the benefit provided from the use of uterine muscle relaxant drugs (Lede 2005), Chinese herbal medicine (Li 2012), hormones (Devaseelan 2010; Haas 2013; Lim 1013; Morley 2013), and immunotherapy (Wong 2014).

Description of the intervention

Vitamins are essential nutrients required in the body for numerous functions such as to ensure normal metabolism, physical growth and development as well as to prevent diseases. Based on evidence from observational studies, vitamin supplementation has been advocated for the prevention of miscarriage (Hasan 2009; Maconochie 2007), most commonly folate and B vitamins. Due to consistent associations between pregnancy complications and decreased antioxidant defence and infections, it has been suggested that vitamin supplementation during pregnancy might provide protection against adverse pregnancy outcomes and may influence the risk of spontaneous miscarriage in women.

How the intervention might work

Vitamins are either water soluble – such as vitamin C and the B group vitamins (including folate) or fat soluble such as vitamins A, D, E and K. They may be obtained directly from the diet or in the form of dietary supplements of either individual vitamin or multivitamin preparations. Multivitamins contain a range of vitamins and minerals, usually in doses similar to the recommended dietary intakes.

The rationale for vitamin supplementation for the prevention of miscarriage is based on epidemiological studies linking healthy dietary patterns with reduced risk for miscarriage (Hasan 2009; Maconochie 2007). Several studies have reported an association between certain vitamin deficiencies and adverse reproductive outcomes (George 2002; Guerra-Shinohara 2010; Hübner 2008; Reznikoff-Etiévant 2002). Nutritional mechanisms underlying this association include homocysteine metabolism and oxidative stress.

Homocysteine is an amino acid that is involved in several key metabolic processes, vital to ongoing cellular activity of the living organism. The metabolism of homocysteine is facilitated by B vitamins and folate. The concentration of homocysteine in the blood is determined by various dietary factors, including folate, vitamin B6 and vitamin B12. Disturbance of maternal and fetal homocysteine metabolism has been associated with various obstetric conditions including miscarriage (Hague 2003; Nelen 2000), and hyperhomocysteinaemia is considered a risk factor for recurrent early pregnancy loss. Therefore, supplementation with B vitamins and folate may influence the risk of spontaneous miscarriage in women with recurrent miscarriage. Moreover, low serum vitamin B12 concentrations have been reported in women with recurrent miscarriage (Hübner 2008). Evidence on the effect of vitamin supplementation, particularly folic acid, on risk of miscarriage is still conflicting; however the few studies that have adjusted for confounding support a protective effect.

Oxidative stress is caused by an imbalance between pro-oxidants and antioxidants. Pro-oxidants act either by generating reactive oxygen species (ROS) or by inhibiting antioxidant systems. In living cells, ROS are formed continuously both from biochemical processes occurring in the body and in reaction to external factors. Excessive ROS production may however, overpower the body's natural antioxidant defence system, creating an environment unsuitable for normal female reproductive processes (Al-Gubory 2010). A recent review of evidence from experimental and observational studies suggests that oxidative stress is an important cause in spontaneous and recurrent miscarriage (Agarwal 2012b; Al-Gubory 2010; Gupta 2007). Adequate maternal antioxidant status before and during pregnancy could prevent and control oxidative stress. Therefore, intake of antioxidant vitamins such as vitamin C and vitamin E may be an important factor to reduce the risk of miscarriage. In a population-based case-control study, vitamin supplementation (including vitamin C), and eating fresh fruits and vegetables daily were associated with reduced risk of miscarriage (Maconochie 2007). Another observational study demonstrated an association between the risk of spontaneous early miscarriage and dietary factors; poor intake of green vegetables, fruit and dairy products coupled with a high intake of fat was associated with a high risk of spontaneous miscarriage (Di Cintio 2001). There is limited information available about the impact of vitamins on the risk of early versus late miscarriage. However, dietary factors could theoretically influence structural abnormalities such as cervical incompetence. There is a growing body of research investigating the relationship between nutrition and placental development, fetal growth, pregnancy outcomes and adult diseases (McMillen 2008; Meher 2015; Wu 2004). Therefore, adequate maternal nutrition, particularly vitamin intake, may be an important factor in preventing spontaneous miscarriage. Currently, little information is available about the most appropriate vitamin type or combination. Similarly, many commercially available

vitamin preparations contain a range of combinations of vitamins. Therefore, this review will cover all vitamin types.

Why it is important to do this review

Vitamin supplementation is frequently recommended for pregnant women and women planning to conceive. The documented benefits of supplementation relate mainly to the lowered risk of congenital anomalies such as neural tube defects (Hovdenak 2012; MRC Vitamin Study Research Group 1991). Given the widespread vitamin supplementation before and during pregnancy, studying the relationship between this common exposure and early pregnancy outcomes is of great value, particularly since the causes of miscarriage are unknown and this exposure is known to affect specific developmental processes.

This is an update of a Cochrane review first published in 2005 and previously updated in 2011. The previously updated review included 28 trials involving 96,674 women (98,267 pregnancies (Rumbold 2011)). Based on available evidence, Rumbold 2011 concluded that taking any vitamin supplements prior to pregnancy or in early pregnancy does not prevent women from experiencing miscarriage or stillbirth. However, there is insufficient evidence to examine the effects of different combinations of vitamins on miscarriage. In the current review, we examined the effect of different vitamin combinations on the risk of miscarriage. The scope of the current update has been restricted to look at miscarriage and miscarriage-related outcomes.

OBJECTIVES

1. To determine the effectiveness and safety of any vitamin supplementation taken by women prior to conception, periconceptionally and in early pregnancy on the risk of spontaneous miscarriage.
2. If vitamins are effective, to determine which of these agents are best and to compare vitamins with other interventions.

METHODS

Criteria for considering studies for this review

Types of studies

All randomised trials (including individual- and cluster-randomised) and quasi-randomised trials comparing one or more vitamins with either placebo, other vitamins, no vitamins or other interventions, prior to conception, periconceptionally or in early to mid pregnancy. Cross-over trials were not included.

Types of participants

Pregnant women (less than 20 weeks' gestation) or women in the reproductive age group planning on becoming pregnant in the near future, regardless of whether they are at low or high risk of having a miscarriage. No restrictions were placed on the age of participants or past obstetric history.

Types of interventions

Comparisons of specific vitamin(s), alone or in combination with other agents with either placebo, other vitamin(s), no vitamin(s) or other interventions for the prevention of miscarriage, either in areas where there is an inadequate dietary intake or where there is a presumed adequate intake of that vitamin(s).

The review authors deemed it important to include any supplementation trials, where supplementation began prior to 20 weeks' gestation, and where at least one miscarriage-related outcome as specified in the review was reported, even if the intervention was not specifically for the prevention of miscarriage. We excluded trials where the onset of supplementation occurred definitely after 20 weeks' gestation or where it was reported that the majority of women commenced supplementation after 20 weeks' gestation. We included trials where the onset of supplementation occurred both prior to and after 20 weeks' gestation, and when it could not be established whether the majority of the women started supplementation prior to 20 weeks' gestation.

Types of outcome measures

The scope of the current update has been restricted to look at miscarriage and miscarriage-related outcomes.

Primary outcomes

1. Total fetal loss, defined as the combined numbers of early miscarriage (spontaneous pregnancy loss less than 12 weeks' gestation), late miscarriage (spontaneous pregnancy loss greater than or equal to 12 and less than 24 weeks), and stillbirth (pregnancy loss at greater than or equal to 24 weeks).
2. Early or late miscarriage.

To overcome wide variation in the definitions of miscarriage and stillbirth between studies, we included the combined outcome 'total fetal loss' in the review.

Secondary outcomes

1. Stillbirth.
2. Congenital malformations.
3. Adverse effects of vitamin supplementation sufficient to stop supplementation, such as manifestations of hypervitaminosis, headache, nausea, vomiting, diarrhoea

Search methods for identification of studies

The following methods section of this review is based on a standard template used by the Cochrane Pregnancy and Childbirth Group.

Electronic searches

We searched the Cochrane Pregnancy and Childbirth Group's Trials Register by contacting the Trials Search Co-ordinator (6 November 2015).

The Register is a database containing over 21,000 reports of controlled trials in the field of pregnancy and childbirth. For full search methods used to populate the Pregnancy and Childbirth Group's Trials Register including the detailed search strategies for CENTRAL, MEDLINE, Embase and CINAHL; the list of handsearched journals and conference proceedings, and the list of journals reviewed via the current awareness service, please follow this link to the editorial information about the Cochrane Pregnancy and Childbirth Group in *The Cochrane Library* and select the '***Specialized Register*** ' section from the options on the left side of the screen.

Briefly, the Cochrane Pregnancy and Childbirth Group's Trials Register is maintained by the Trials Search Co-ordinator and contains trials identified from:

1. monthly searches of the Cochrane Central Register of Controlled Trials (CENTRAL);
2. weekly searches of MEDLINE (Ovid);
3. weekly searches of Embase (Ovid);
4. monthly searches of CINAHL (EBSCO);
5. handsearches of 30 journals and the proceedings of major conferences;
6. weekly current awareness alerts for a further 44 journals plus monthly BioMed Central email alerts.

Search results are screened by two people and the full text of all relevant trial reports identified through the searching activities described above is reviewed. Based on the intervention described, each trial report is assigned a number that corresponds to a specific Pregnancy and Childbirth Group review topic (or topics), and is then added to the Register. The Trials Search Co-ordinator searches the Register for each review using this topic number rather than keywords. This results in a more specific search set which has been fully accounted for in the relevant review sections (Included studies; Excluded studies; Studies awaiting classification; Ongoing studies).

[We carried out additional author searching in an earlier version of this review (Rumbold 2005), *see* Appendix 1 for details]

Searching other resources

We searched the reference lists of retrieved studies.

We did not apply any language or date restrictions.

Data collection and analysis

For methods used in the previous version of this review, see Rumbold 2011.

For this update, the following methods were used for assessing the 90 reports that were identified as a result of the updated search.

The following methods section of this review is based on a standard template used by the Cochrane Pregnancy and Childbirth Group.

Selection of studies

Two review authors independently assessed all the potential studies identified as a result of the search strategy for inclusion. Disagreements were resolved through discussion and, when required, we consulted a third person. We created a study flow diagram to map out the number of records identified, included and excluded.

Data extraction and management

We collected data from the selected studies using a pre-designed data extraction form. For eligible studies, two review authors extracted the data using the agreed form. We resolved discrepancies through discussion. If discrepancies could not be resolved, we consulted a third review author. We entered data into Review Manager software (RevMan 2014) and checked for accuracy. When information regarding any of the above was unclear, we attempted to contact authors of the original reports to provide further details.

Assessment of risk of bias in included studies

Two review authors independently assessed risk of bias for each study using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We resolved any disagreement by discussion or by involving a third assessor.

(1) Random sequence generation (checking for possible selection bias)

We describe for each included study the method used to generate the allocation sequence in sufficient detail to allow an assessment of whether it should produce comparable groups.

We assessed the method as:

- low risk of bias (any truly random process, e.g. random number table; computer random number generator);
- high risk of bias (any non-random process, e.g. odd or even date of birth; hospital or clinic record number);
- unclear risk of bias.

(2) Allocation concealment (checking for possible selection bias)

We describe for each included study the method used to conceal allocation to interventions prior to assignment and assessed whether intervention allocation could have been foreseen in advance of, or during recruitment, or changed after assignment.

We assessed the methods as:

- low risk of bias (e.g. telephone or central randomisation; consecutively numbered sealed opaque envelopes);
- high risk of bias (open random allocation; unsealed or non-opaque envelopes, alternation; date of birth);
- unclear risk of bias.

(3.1) Blinding of participants and personnel (checking for possible performance bias)

We describe for each included study the methods used, if any, to blind study participants and personnel from knowledge of which intervention a participant received. We considered that studies were at low risk of bias if they were blinded, or if we judged that the lack of blinding would be unlikely to affect results. We assessed blinding separately for different outcomes or classes of outcomes.

We assessed the methods as:

- low, high or unclear risk of bias for participants;
- low, high or unclear risk of bias for personnel.

(3.2) Blinding of outcome assessment (checking for possible detection bias)

We describe for each included study the methods used, if any, to blind outcome assessors from knowledge of which intervention a participant received. We assessed blinding separately for different outcomes or classes of outcomes.

We assessed methods used to blind outcome assessment as:

- low, high or unclear risk of bias.

(4) Incomplete outcome data (checking for possible attrition bias due to the amount, nature and handling of incomplete outcome data)

We describe for each included study, and for each outcome or class of outcomes, the completeness of data including attrition and exclusions from the analysis. We state whether attrition and exclusions were reported and the numbers included in the analysis at each stage (compared with the total randomised participants), reasons for attrition or exclusion where reported, and whether missing data were balanced across groups or were related to outcomes. Where sufficient information was reported, or supplied by the trial authors, we re-included missing data in the analyses which we undertook.

We assessed methods as:

- low risk of bias (e.g. no missing outcome data; missing outcome data balanced across groups);
- high risk of bias (e.g. numbers or reasons for missing data imbalanced across groups; 'as treated' analysis done with substantial departure of intervention received from that assigned at randomisation);
- unclear risk of bias.

(5) Selective reporting (checking for reporting bias)

We describe for each included study how we investigated the possibility of selective outcome reporting bias and what we found.

We assessed the methods as:

- low risk of bias (where it is clear that all of the study's pre-specified outcomes and all expected outcomes of interest to the review have been reported);
- high risk of bias (where not all the study's pre-specified outcomes have been reported; one or more reported primary outcomes were not pre-specified; outcomes of interest are reported incompletely and so cannot be used; study fails to include results of a key outcome that would have been expected to have been reported);
- unclear risk of bias.

(6) Other bias (checking for bias due to problems not covered by (1) to (5) above)

We describe for each included study any important concerns we have about other possible sources of bias.

We assessed whether each study was free of other problems that could put it at risk of bias:

- low risk of other bias;
- high risk of other bias;
- unclear whether there is risk of other bias.

(7) Overall risk of bias

We made judgements about whether studies were at high risk of bias, according to the criteria given in the *Handbook* (Higgins 2011). With reference to (1) to (6) above, we assessed the likely magnitude and direction of the bias and whether we considered it was likely to impact on the findings. We explored the impact of the level of bias through undertaking sensitivity analyses - *see* Sensitivity analysis.

Assessment of the quality of the evidence using the GRADE approach

For this update, we assessed the quality of the evidence using the GRADE approach as outlined in the GRADE handbook in order to assess the quality of the body of evidence relating to the following outcomes in the comparisons: 1) vitamin C and vitamin E versus placebo, 2) vitamin A plus iron plus folate versus iron plus folate and 3) multivitamin plus iron plus folate versus iron plus folate.

1. Total fetal loss, defined as the combined numbers of early miscarriage (spontaneous pregnancy loss less than 12 weeks' gestation), late miscarriage (spontaneous pregnancy loss greater than or equal to 12 and less than 24 weeks), and stillbirth (pregnancy loss at greater than or equal to 24 weeks).
2. Early or late miscarriage.
3. Stillbirth.
4. Adverse effects of vitamin supplementation sufficient to stop supplementation.

We used the GRADEpro Guideline Development Tool to import data from Review Manager 5.3 (RevMan 2014) in order to create 'Summary of findings' tables. A summary of the intervention effect and a measure of quality for each of the above outcomes was produced using the GRADE approach. The GRADE approach uses five considerations (study limitations, consistency of effect, imprecision, indirectness and publication bias) to assess the quality of the body of evidence for each outcome. The evidence was downgraded from 'high quality' by one level for serious (or by two levels for very serious) limitations, depending on assessments for risk of bias, indirectness of evidence, serious inconsistency, imprecision of effect estimates or potential publication bias.

Measures of treatment effect

Dichotomous data

For dichotomous data, we present results as summary risk ratio (RR) with 95% confidence intervals (CI).

Continuous data

For continuous data, we planned to use the mean difference (MD) if outcomes were measured in the same way between trials and, if appropriate, the standardised mean difference (SMD) to combine trials that measured the same outcome, but used different methods.

Unit of analysis issues

Where trials recruited women prior to becoming pregnant, we reported the denominators for each trial as all women randomised; or where there was accurate information about the number of women in each trial who became pregnant, we reported the denominators as the number of women randomised with confirmed pregnancy.

We included all included trials in the initial analysis which we performed by any vitamin to include all vitamin combinations and then by individual vitamin type.

Cluster-randomised trials

We included cluster-randomised trials in the analyses along with individually-randomised trials. We used the effect estimates and

uncertainty range from the cluster trials to perform the meta-analysis using the generic inverse variance approach for the meta-analysis of dichotomous outcomes where trials using cluster-randomisation techniques were included (Alderson 2004).

Dealing with missing data

For included studies, we noted levels of attrition. We explored the impact of including studies with high levels of missing data in the overall assessment of treatment effect by using sensitivity analysis.

For all outcomes, we carried out analyses, as far as possible, on an intention-to-treat basis, i.e. we attempted to include all participants randomised to each group in the analyses, and all participants were analysed in the group to which they were allocated, regardless of whether or not they received the allocated intervention. The denominator for each outcome in each trial was the number randomised minus any participants whose outcomes were known to be missing.

Assessment of heterogeneity

We applied tests of heterogeneity between trials to assess the significance of any differences between trials in the analyses. We regarded heterogeneity as substantial if the I^2 was greater than 30% and either the Tau^2 was greater than zero, or there was a low P value (less than 0.10) in the Chi^2 test for heterogeneity.

Assessment of reporting biases

We investigated reporting biases (such as publication bias) using funnel plots. We assessed funnel plot asymmetry visually. If asymmetry was suggested by a visual assessment, we performed exploratory analyses to investigate it.

Data synthesis

We carried out statistical analysis using the Review Manager software (RevMan 2014). We used fixed-effect meta-analysis for combining data where it was reasonable to assume that studies were estimating the same underlying treatment effect: i.e. where trials were examining the same intervention, and the trials' populations and methods were judged sufficiently similar. If there was clinical heterogeneity sufficient to expect that the underlying treatment effects differed between trials, or if substantial statistical heterogeneity was detected, we used random-effects meta-analysis to produce an overall summary, if an average treatment effect across trials was considered clinically meaningful. We treated the random-effects summary as the average of the range of possible treatment effects and we discuss the clinical implications of treatment effects differing between trials. If the average treatment effect was not clinically meaningful, we did not combine trials. Where we used random-effects analyses, we have presented the results as the average treatment effect with 95% confidence intervals, and the estimates of Tau^2 and I^2.

Subgroup analysis and investigation of heterogeneity

Had we identified substantial heterogeneity, we planned to investigate it using subgroup analyses and sensitivity analyses and to consider whether an overall summary was meaningful, and if it was, to use random-effects analysis to produce it.

In this update, we were not able to carry out the following subgroup analyses:

1. the dose of vitamin(s) (below or above the recommended dietary intake); and the duration of vitamin usage, based on time of trial entry: before pregnancy, < 12 weeks' gestation, between 12-20 weeks' gestation or 'mixed', which included women enrolled before and after 20 weeks' gestation;
2. their risk of spontaneous miscarriage (high risk defined as the presence of medical conditions associated with miscarriage such as hyperhomocysteinaemia, thrombophilia, antiphospholipid syndrome, systemic lupus erythematosus; low risk defined as none of the above conditions); their risk of recurrent miscarriage (high risk defined as two or more previous consecutive spontaneous miscarriages, and/or the presence of medical conditions associated with miscarriage such as hyperhomocysteinaemia, thrombophilia, antiphospholipid syndrome, systemic lupus erythematosus; low risk defined as none of the above conditions);
3. low or adequate dietary vitamin intake at trial entry (low intake defined as less than the recommended daily intake for each vitamin in that setting, as measured by dietary questionnaire).

We would have included all outcomes in the subgroup analysis.

We planned to assess subgroup differences by interaction tests available within RevMan (RevMan 2014) and to report the results of subgroup analyses quoting the Chi^2 statistic and P value, and the interaction test I^2 value.

Sensitivity analysis

We carried out sensitivity analysis to explore the effects of trial quality and type of randomisation on the primary outcomes related to fetal loss (total fetal loss and early or late miscarriage). We included only trials with 'adequate' rating on allocation concealment, We considered these trials to be of high quality. We also carried out sensitivity analysis by excluding cluster-randomised trials and comparing the results of cluster-randomised trials with the individually-randomised trials.

RESULTS

Description of studies

See tables Characteristics of included studies and Characteristics of excluded studies for details of individual studies.

Included studies

For the 2016 update, we included a total of 40 trials (involving 276,820 women) assessing supplementation with specific vitamin(s) starting prior to 20 weeks' gestation. Many of the trials assessed interventions not specifically for the prevention of miscarriage, however, the authors included any supplementation trials, where supplementation began prior to 20 weeks' gestation, and where at least one miscarriage-related outcome as specified in the review was reported.

Participants

The demographic and obstetric characteristics of the women varied widely between the trials (see table Characteristics of included studies). The 40 included trials contributed data for analysis from 276,820 women. Eight of the 40 included studies were cluster-randomised trials including 217,726 women (Bhutta 2009; Katz 2000; Summit 2008; Sunawang 2009; West 2011; West 2014; Zagre 2007; Zeng 2008). Two of the trials from the previous

version of this review (one cluster (Katz 2000), and one small trial (Roberfroid 2008)) included women who were pregnant more than once in the study period; resulting in data contributing to 59,146 pregnancies for the individual trials and 219,267 pregnancies from the cluster trials. Five trials enrolled women prior to conception (Czeizel 1994; Hemmi 2003; ICMR 2000; Kirke 1992; MRC 1991) and asked women to continue taking the supplements up until the second or third missed menstrual period. One trial (Katz 2000) supplemented women from before conception, through pregnancy and postpartum for a total of 3.5 years postpartum. Another eight trials enrolled women in the first trimester (Briscoe 1959; Hans 2010; Rumiris 2006; Tofail 2008; West 2011; West 2014; Wibowo 2012; Zagre 2007), and 24 trials in early to mid pregnancy (Bhutta 2009; Chappell 1999; Fawzi 1998; Fawzi 2007; Fleming 1968; Fleming 1986; Kumwenda 2002; McCance 2010; Osrin 2005; People's League 1942; Poston 2006; Prawirohartono 2011; Roberfroid 2008; Roberts 2010; Rumbold 2006; Rush 1980; Schmidt 2001; Spinnato 2007; Steyn 2003; Sunawang 2009; Van den Broek 2006; Villar 2009; Xu 2010; Zeng 2008). Some of the trials enrolling women in early to mid pregnancy included women enrolled at or after 20 weeks' gestation (Chappell 1999; Fawzi 1998; Fawzi 2007; Fleming 1968; Fleming 1986; Kumwenda 2002; McCance 2010; Osrin 2005; People's League 1942; Roberfroid 2008; Rumbold 2006; Rush 1980; Schmidt 2001; Spinnato 2007; Steyn 2003; Van den Broek 2006; Villar 2009; Zeng 2008). One trial (Summit 2008), enrolled 41,839 women at 'any gestational age', although more than 70% of the women were enrolled in the first or second trimester.

Two trials (Fawzi 1998; Kumwenda 2002) involved vitamin A supplementation in women seropositive for the Human Immunodeficiency Virus (HIV); one trial (Poston 2006) involved only women with clinical risk factors for pre-eclampsia, while one trial (McCance 2010), limited the eligibility to women with type1 diabetes. Roberts 2010 involved only nulliparous women.

Baseline characteristics of women enrolled in the intervention group and control group were comparable in all the trials except two (Xu 2010; Zagre 2007). In Xu 2010, there was a slightly higher proportion of women with multiple pregnancies in the placebo group; while in Zagre 2007, women in the control group tended to be poorer and less educated, while women in the intervention group had larger households and used more preventive measures against malaria.

The trials were conducted in both resource-rich and resource-poor countries including the United States (Briscoe 1959; Roberts 2010; Rush 1980), Canada (Xu 2010), the United Kingdom (Chappell 1999; McCance 2010; People's League 1942; Poston 2006), Hungary (Czeizel 1994), Tanzania (Fawzi 1998; Fawzi 2007), Nigeria (Fleming 1968; Fleming 1986), Burkino Faso (Roberfroid 2008), Japan (Hemmi 2003), India (ICMR 2000), Nepal (Katz 2000; Osrin 2005), the Republic of Ireland (Kirke 1992), Uganda (Hans 2010), Bangladesh (West 2011; West 2014, Tofail 2008), China (Zeng 2008), Niger (Zagre 2007), Pakistan (Bhutta 2009), Australia (Rumbold 2006), Brazil (Spinnato 2007), Mexico (Xu 2010), Malawi (Kumwenda 2002; Van den Broek 2006), Indonesia (Prawirohartono 2011; Rumiris 2006; Schmidt 2001; Sunawang 2009; Summit 2008; Wibowo 2012), and South Africa (Steyn 2003). One trial involved 33 international centres (MRC 1991) and another trial was a multi-country study involving India, Peru, South Africa and Vietnam (Villar 2009).

Interventions

The 40 trials assessed a range of vitamin supplements, alone or in combination with other supplements. The vitamins included vitamin A, alone or with iron, folic acid, multivitamins, or β-carotene (Fawzi 1998; Katz 2000; Kumwenda 2002; Prawirohartono 2011; Schmidt 2001; Van den Broek 2006; West 2011); vitamin C with or without multivitamins or vitamin E (Briscoe 1959; Chappell 1999; Hans 2010; Hemmi 2003; McCance 2010; Poston 2006; Roberts 2010; Rumbold 2006; Spinnato 2007; Steyn 2003; Villar 2009; Xu 2010); folic acid with or without multivitamins and/or iron (Czeizel 1994; Fleming 1968; Fleming 1986; ICMR 2000; Kirke 1992; MRC 1991); antioxidant vitamins (Wibowo 2012); multivitamins with/without folic acid, vitamin A, vitamin E or iron and folic acid (Bhutta 2009; Czeizel 1994; Fawzi 1998; Fawzi 2007; ICMR 2000; Kirke 1992; MRC 1991; Osrin 2005; Roberfroid 2008; Rumiris 2006; Rush 1980; Sunawang 2009; Summit 2008; Tofail 2008; West 2014; Zagre 2007; Zeng 2008); and multivitamins alone (People's League 1942; Rush 1980). The doses of vitamins were similar for the vitamin C supplementation trials (range 400 mg to 1000 mg). However, they varied widely between trials for the folic acid (range 0.3 mg to 10 mg), multivitamins and vitamin A trials (range 5000 international units (IU) to 23,300 IU). The components of MMN supplementation were different among the trials but all of them contained iron and folate in the MMN supplements. All supplements were taken orally from the enrolment until delivery or up to 3.5 years postpartum.

Outcomes

Main outcomes

Thirty-six trials reported pregnancy loss as miscarriage or stillbirth. The outcome 'total fetal loss' included both miscarriage or stillbirth, and overcame problems with different definitions of miscarriage and stillbirth. There was no consistency amongst trials with regards to the definition of miscarriage. For some trials, miscarriage was considered to occur up until 26 or 28 weeks' gestation, while other studies reported miscarriage as pregnancy loss prior to 20 weeks' gestation. Other studies did not specify their definition of miscarriage or stillbirth.

Other outcomes

There was no consistency amongst trials with regards to the definition of stillbirth. In some trials, stillbirth was considered as pregnancy loss greater than or equal to 20 weeks' gestation, while some trials considered stillbirth as pregnancy loss beyond 24 weeks' gestation. Thirty trials reported stillbirth as an outcome. Only one trial (Spinnato 2007) reported on adverse effects of vitamin sufficient to stop supplementation, while congenital malformations was reported in nine trials (Czeizel 1994; Kirke 1992; McCance 2010; MRC 1991; Osrin 2005; Poston 2006; Spinnato 2007; Villar 2009; Xu 2010).

Excluded studies

We excluded 48 trials, of which 16 trials reported no clinically relevant data, or data in a format suitable for inclusion (Christian 2003; Chelchowska 2004; Correia 1982; Hibbard 1969; Laurence 1981; Lira 1989; Meirinho 1987; Mock 2002; Moldenhauer 2002; Semba 2001; Suharno 1993; Tanumihardjo 2002; Taylor 1982; Thauvin 1992; Villamor 2002; Vutyavanich 1995). Seven trials did not clearly report the gestational age when supplementation was started (Biswas 1984; Fletcher 1971; Hampel 1974; Lumeng 1976; Schuster 1984; Trigg 1976; Young 2015), and for two trials, the

majority of women were enrolled after 20 weeks and did not report outcomes separately for women starting supplementation prior to 20 weeks (Ferguson 1955; Giles 1971). Thirteen trials (Baumslag 1970; Blot 1981; Chanarin 1968; Colman 1974; Coutsoudis 1999; Dawson 1962; Edelstein 1968; Feyi-Waboso 2005; Hankin 1966; Kaestel 2005; Marya 1981; Metz 1965; Owen 1966) reported supplementation after 20 weeks' gestation. One trial (Ross 1985) did not specify the contents of the supplements; in five trials all women were given a vitamin supplement (Hekmatdoost 2011; Hunt 1984; Huybregts 2009; Shu 2002; Wehby 2012); one trial was a food intervention (Potdar 2014) and two were non-randomised (Smithells 1981; Ulrich 1999).

Three other trials (Beazley 2005; Chaudhuri 1969; Rivas-Echeverria 2000) supplemented women for the prevention of pre-eclampsia, and did not report any outcomes related to pregnancy loss. These trials are covered in the Cochrane review '*Antioxidants for preventing pre-eclampsia*' (Rumbold 2008).

Risk of bias in included studies

Figure 1 and Figure 2 illustrate that the trials were of variable quality. Two trials (Fleming 1968; People's League 1942) used quasi-random allocation methods involving alternate allocation of participants. Similarly, eight trials (Bhutta 2009; Katz 2000; Summit 2008; Sunawang 2009; West 2011; West 2014; Zagre 2007; Zeng 2008) used cluster randomisation.

Figure 1. 'Risk of bias' graph: review authors' judgements about each risk of bias item presented as percentages across all included studies

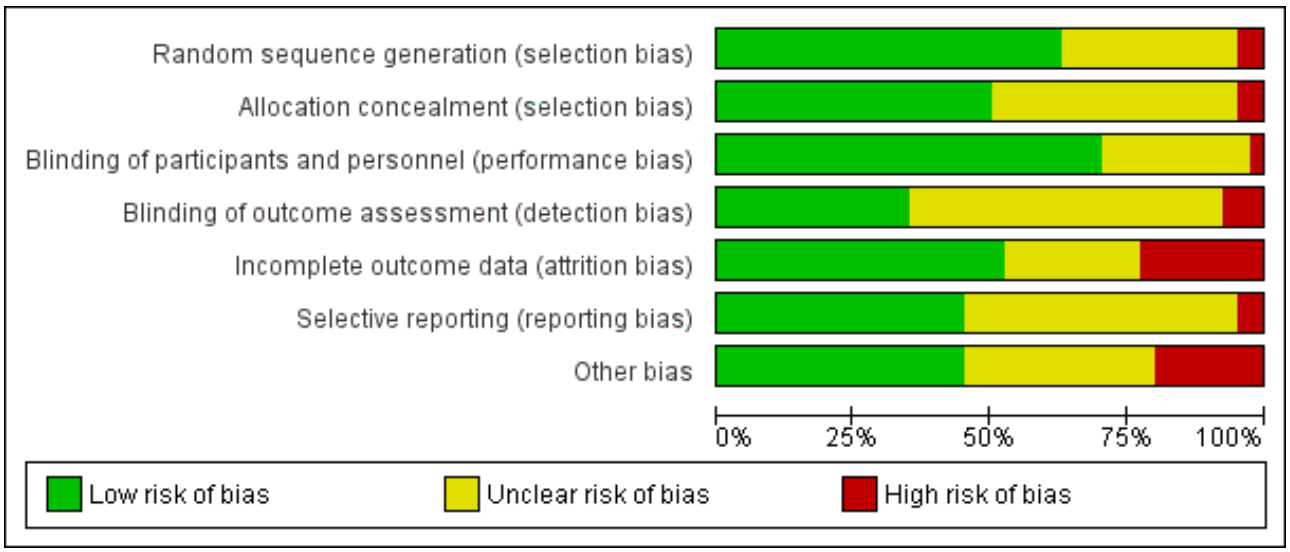


Figure 2. 'Risk of bias' summary: review authors' judgements about each risk of bias item for each included study

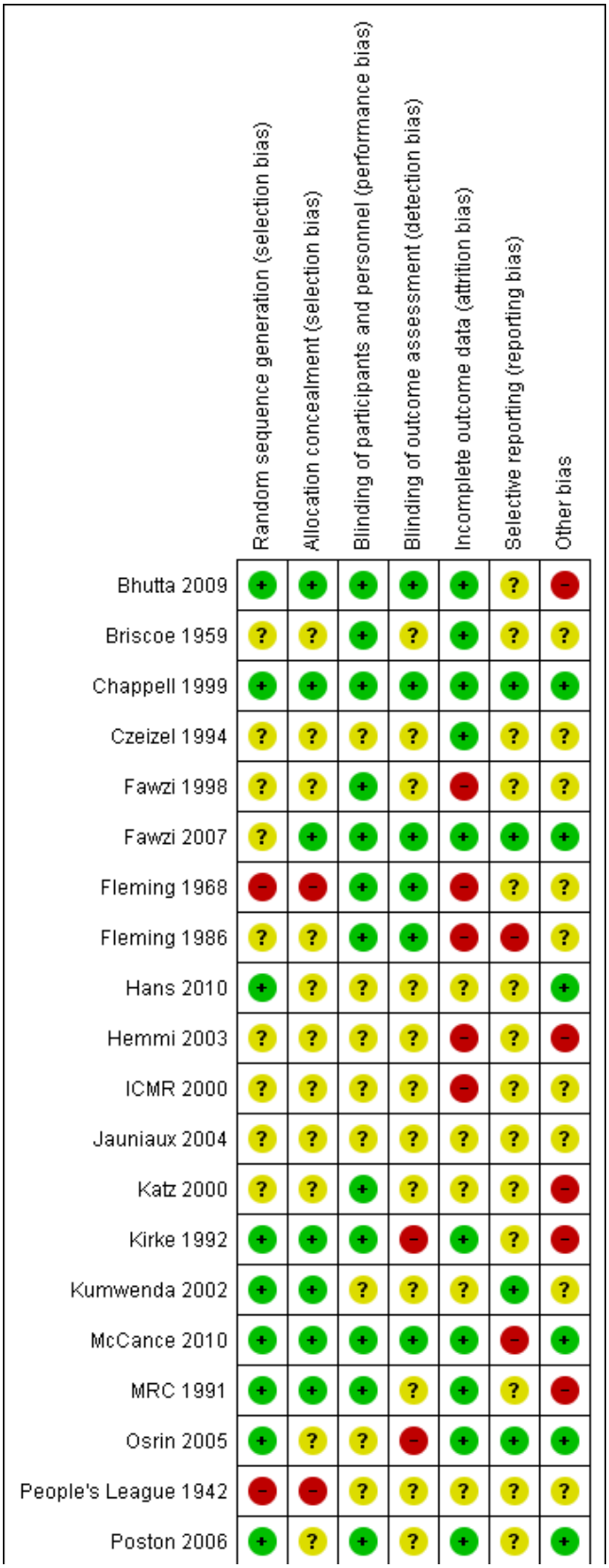
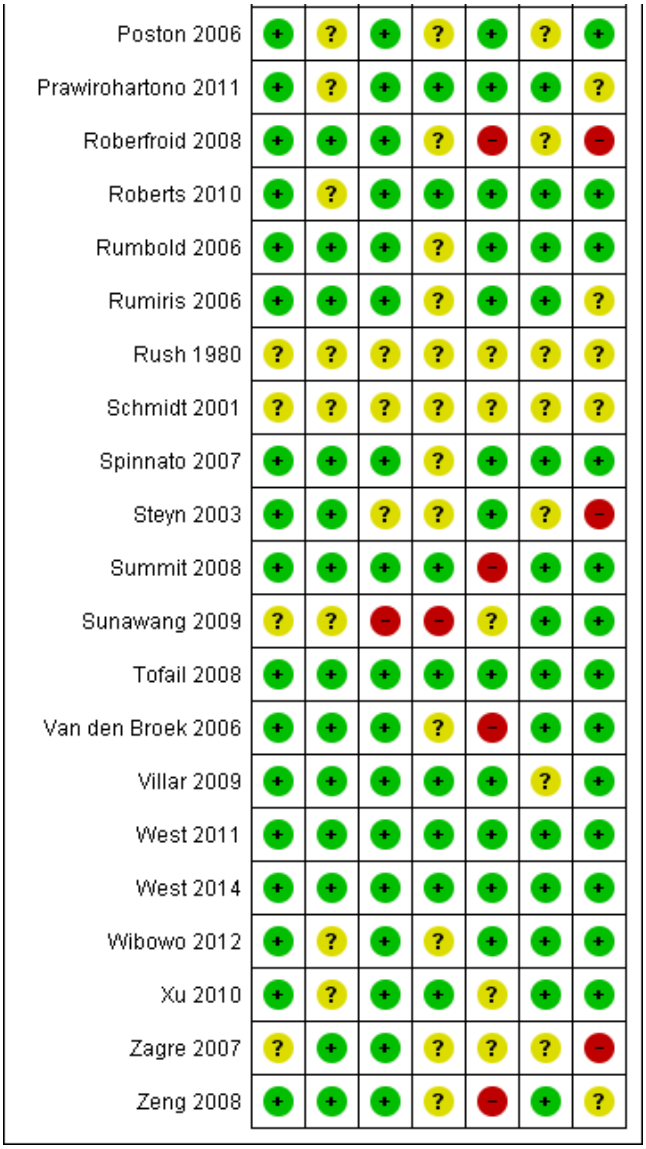


Figure 2. (Continued)



Allocation

Sequence generation: 25 trials adequately randomised the participants to the intervention and control groups and were judged to be of low risk of bias (Bhutta 2009; Chappell 1999; Hans 2010; Kirke 1992; Kumwenda 2002; McCance 2010; MRC 1991; Osrin 2005; Poston 2006; Prawirohartono 2011; Roberfroid 2008; Roberts 2010; Rumbold 2006; Rumiris 2006; Spinnato 2007; Steyn 2003; Summit 2008; Tofail 2008; Van den Broek 2006; Villar 2009; West 2011; West 2014; Wibowo 2012; Xu 2010; Zeng 2008). The method used for random sequence generation was unclear in 13 trials (Briscoe 1959; Czeizel 1994; Fawzi 1998; Fawzi 2007; Fleming 1986; Hemmi 2003; ICMR 2000; Jauniaux 2004; Katz 2000; Rush 1980; Schmidt 2001; Sunawang 2009; Zagre 2007), because methodological details were not reported or not clearly described. The remaining two trials Fleming 1968 and People's League 1942 used quasi-randomised methods and were rated as high risk of bias for sequence generation.

Allocation concealment: 20 trials were assessed to have a low risk of bias for adequate concealment of participants to treatment and control groups (Bhutta 2009; Chappell 1999; Fawzi 2007; Kirke 1992; Kumwenda 2002; McCance 2010; MRC 1991; Roberfroid 2008; Rumbold 2006; Rumiris 2006; Spinnato 2007; Steyn 2003; Summit 2008; Tofail 2008; Van den Broek 2006; Villar 2009; West 2011; West 2014; Zagre 2007; Zeng 2008). In 18 trials the method for allocation concealment was not described or not clearly described (Briscoe 1959; Czeizel 1994; Fawzi 1998; Fleming 1986; Hans 2010; Hemmi 2003; ICMR 2000; Jauniaux 2004; Katz 2000; Osrin 2005; Poston 2006; Prawirohartono 2011; Roberts 2010; Rush 1980; Schmidt 2001; Sunawang 2009; Wibowo 2012; Xu 2010). In two trials, allocation was not concealed and therefore judged as high risk of bias (Fleming 1968; People's League 1942).

Blinding

Participants and personnel: 28 trials were assessed as having a low risk of performance bias and reported blinding of participants and personnel to the treatment allocation (Bhutta 2009; Briscoe

1959; Chappell 1999; Fawzi 1998; Fawzi 2007; Fleming 1968; Fleming 1986; Katz 2000; Kirke 1992; McCance 2010; MRC 1991; Poston 2006; Prawirohartono 2011; Roberfroid 2008; Roberts 2010; Rumbold 2006; Rumiris 2006; Spinnato 2007; Summit 2008; Tofail 2008; Van den Broek 2006; Villar 2009; West 2011; West 2014; Wibowo 2012; Xu 2010; Zagre 2007; Zeng 2008). Another 11 trials were judged to have an unclear risk of bias because no or not enough information were provided (Czeizel 1994; Hans 2010; Hemmi 2003; ICMR 2000; Jauniaux 2004; Kumwenda 2002; Osrin 2005; People's League 1942; Rush 1980; Schmidt 2001; Steyn 2003). Sunawang 2009 was rated as high risk of bias as personnel (but not participants) were aware of participants' allocation due to the different appearance of the supplements.

Outcome assessment: blinding of outcome assessors was clearly stated in 14 trials (Bhutta 2009; Chappell 1999; Fawzi 2007; Fleming 1968; Fleming 1986; McCance 2010; Prawirohartono 2011; Roberts 2010; Summit 2008; Tofail 2008; Villar 2009; West 2011; West 2014; Xu 2010) and unclear in 23 trials (Briscoe 1959; Czeizel 1994; Fawzi 1998; Hans 2010; Hemmi 2003; ICMR 2000; Jauniaux 2004; Katz 2000; Kumwenda 2002; MRC 1991; People's League 1942; Poston 2006; Roberfroid 2008; Rumbold 2006; Rumiris 2006; Rush 1980; Schmidt 2001; Spinnato 2007; Steyn 2003; Van den Broek 2006; Wibowo 2012; Zagre 2007; Zeng 2008). In Kirke 1992; Osrin 2005 and Sunawang 2009 outcome assessors were not blinded to the allocation code and the trials were rated as high risk of detection bias.

Incomplete outcome data

Loss to follow-up ranged from no loss at all in Briscoe 1959; Rumbold 2006; Rumiris 2006; Steyn 2003 to over 20% in Fleming 1968; ICMR 2000; Summit 2008 and Van den Broek 2006. Incomplete outcome data was judged low risk of bias in 21 trials and high in nine trials. Ten trials were rated as unclear risk of bias due to missing information about loss of follow-up.

Selective reporting

Eighteen trials were considered to have a low risk of reporting bias. Another 20 trials were assessed as unclear risk of bias because of unavailability of trial registration or protocol (Bhutta 2009; Rush 1980), variations between the protocol and the publication (Poston 2006), due to insufficient details provided about methods or selective reporting (Briscoe 1959; Fleming 1968; Hans 2010; Hemmi 2003; ICMR 2000; Kirke 1992; MRC 1991; People's League 1942; Roberfroid 2008; Steyn 2003; Villar 2009; Zagre 2007), variations of information between serial publications (Czeizel 1994; Fawzi 1998; Katz 2000; Schmidt 2001), or the trial was stopped before completion (Jauniaux 2004). The remaining two trials were at high risk of reporting bias; in Fleming 1986, not all outcomes were reported for all treatment groups and in McCance 2010, fewer outcomes were stated in the trial registration compared with the report.

Other potential sources of bias

In 18 trials, other sources of bias were not detected and these trials were rated as low risk of bias. Fourteen trials provided only limited methodological details to exclude other sources of bias and were judged as unclear (Briscoe 1959; Czeizel 1994; Fawzi 1998; Fleming 1968; Fleming 1986; ICMR 2000; Jauniaux 2004; Kumwenda 2002; People's League 1942; Prawirohartono 2011; Rush 1980; Schmidt 2001) as well as Rumiris 2006, were participants in the control and intervention group slightly differed in systolic blood pressure at baseline. Additionally, Zeng 2008 was rated as unclear due to an imbalanced number of excluded clusters across the intervention groups, which may have been due to important baseline differences. The remaining eight trials were at high risk of bias. In Bhutta 2009, the distribution of study participants across the urban and rural areas is unclear from the text and no adjustments were made for cluster design. In Hemmi 2003, no placebo was used in the control group. Two trials (Katz 2000; Roberfroid 2008) used the total number of pregnancies during the study period as dominator and not the total number or randomised women. In Kirke 1992 and MRC 1991, the trials were terminated at an earlier stage and in Steyn 2003 the outcomes resulted from an interim analysis. In Zagre 2007, the participants in the control and interventions groups differed substantially in their baseline characteristics.

Effects of interventions

See: **Summary of findings for the main comparison** Vitamin C and vitamin E versus placebo for preventing miscarriage; **Summary of findings 2** Vitamin A plus iron plus folate versus iron plus folate for preventing miscarriage; **Summary of findings 3** Multivitamin plus iron plus folate versus iron plus folate for preventing miscarriage

See Summary of findings for the main comparison; Summary of findings 2; Summary of findings 3 for each of the main comparisons. The quality of evidence is included for numerical results of outcomes included in the 'Summary of findings' tables. We have included 40 trials, involving 276,820 women and 278,413 pregnancies. One trial (Jauniaux 2004) contributed no outcome data because it was stopped early and withdrawn. Thus, 39 trials contributed data to our analyses.

Vitamin C supplementation

The trials involving vitamin C supplementation included the following interventions: vitamin C plus multivitamins versus placebo plus multivitamins (Briscoe 1959; Hans 2010), vitamin C and vitamin E supplementation versus placebo (Chappell 1999; McCance 2010; Poston 2006; Roberts 2010; Rumbold 2006; Spinnato 2007; Xu 2010), and vitamin C alone versus no supplement or placebo (Hemmi 2003; Steyn 2003).

Primary outcomes

There was no difference in the risk of **total fetal loss** between women receiving:

1. vitamin C with vitamin E (risk ratio (RR) 1.14, 95% confidence interval (CI) 0.92 to 1.40, seven trials, 18,949 women; Analysis 1.1; *high-quality evidence*);
2. vitamin C alone (RR 1.28, 95% CI 0.58 to 2.83, two trials, 224 women; Analysis 2.1);
3. vitamin C with multivitamins (RR 1.32, 95% CI 0.63 to 2.77, one trial, 406 women; Analysis 3.1);

compared with placebo or no vitamin C groups.

Similarly, we found no overall difference in the risk for **early or late miscarriage** between women receiving:

1. vitamin C with vitamin E (RR 0.97, 95% CI 0.70 to 1.34, five trials, 15,882 women; Analysis 1.2; *moderate-quality evidence*);

2. vitamin C alone (RR 1.17, 95% CI 0.52 to 2.65, two trials, 224 women; Analysis 2.2);
3. vitamin C with multivitamins (RR 1.19, 95% CI 0.79 to 1.79, two trials, 790 women; Analysis 3.2).

Secondary outcomes

There was no difference in the risk of **stillbirth** for women receiving:

1. vitamin C with vitamin E (RR 1.24, 95% CI 0.92 to 1.68, seven trials, 18,906 women; Analysis 1.3; *moderate-quality evidence*);
2. vitamin C alone (RR 3.00, 95% CI 0.12 to 72.77, one trial, 200 women; Analysis 2.3);

compared with placebo or no vitamin C groups. We found no difference in the risk of **congenital malformations** (Analysis 1.4) or **adverse effects of vitamin supplementation** (RR 1.16, 95% CI 0.39 to 3.41, one trial, 739 women; Analysis 1.5; *moderate-quality evidence*).

Vitamin A supplementation

The trials involving vitamin A supplementation included the following interventions: vitamin A and/or beta-carotene versus placebo (Katz 2000; Prawirohartono 2011; West 2011), vitamin A with or without multivitamins versus multivitamins (excluding vitamin A) or placebo (Fawzi 1998), and vitamin A plus iron and folic acid versus iron and folic acid (Kumwenda 2002; Schmidt 2001; Van den Broek 2006).

Primary outcomes

We found no difference in the risk of **total fetal loss** between women receiving:

1. vitamin A plus iron and folate (RR 1.01, 95% CI 0.61 to 1.66, three trials, 1640 women; Analysis 4.1; *low-quality evidence*);
2. vitamin A alone (RR 1.05, 95% CI 0.90 to 1.23, three trials, 52,480 women; $Tau^2 = 0.01$, $I^2 = 73\%$ Analysis 5.1);
3. beta-carotene alone (RR 1.02, 95% CI 0.98 to 1.07, two trials, 51,163 women; Analysis 6.1);
4. vitamin A or beta-carotene (RR 1.05, 95% CI 0.91 to 1.21, one trial, 17,373 women; Analysis 7.1);
5. vitamin A with or without multivitamin (RR 0.80, 95% CI 0.53 to 1.21, one trial, 1074 women; Analysis 8.1);

compared with placebo or no vitamin A groups.

The heterogeneity in Analysis 5.1 seemed to have been contributed by combining two cluster-randomised trials and one individually-randomised trial. Heterogeneity was no longer present when the individually-randomised trial was excluded. However, this did not change the conclusion of no significant difference between vitamin A and no vitamin A groups.

There was no evidence of a difference in the risk for **early or late miscarriage** between women receiving:

1. vitamin A plus iron and folate (RR 0.86, 95% CI 0.46 to 1.62, two trials, 1397 women; Analysis 4.2; *low-quality evidence*);
2. vitamin A alone (RR 0.98, 95% CI 0.92 to 1.04, one trial, 39,668 women; Analysis 5.2);
3. beta-carotene alone (RR 1.00, 95% CI 0.94 to 1.06, one trial, 39,860 women; Analysis 6.2);
4. vitamin A with or without multivitamin (RR 0.76, 95% CI 0.37 to 1.55, one trial, 1075 women; Analysis 8.2);

compared with placebo or no vitamin A groups.

Secondary outcomes

There was no difference in the risk for **stillbirth** for the following supplementation treatments:

1. vitamin A plus iron and folate (RR 1.29, 95% CI 0.57 to 2.91, three trials, 1640 women; Analysis 4.3; *low-quality evidence*);
2. vitamin A alone (RR 0.95, 95% CI 0.86 to 1.06, one trial, 39,668 women; Analysis 5.3);
3. beta-carotene alone (RR 1.09, 95% CI 0.98 to 1.20, one trial, 39,860 women; Analysis 6.3);
4. vitamin A with or without multivitamin (RR 1.04, 95% CI 0.60 to 1.79, one trial, 1075 women; Analysis 8.3);

compared with placebo or no vitamin A groups. **Congenital malformations** and **adverse effects of vitamin supplementation** were not reported by trials included in these analyses.

Multivitamin supplementation

The trials involving multivitamin supplementation included the following interventions: multivitamins with or without folic acid versus no multivitamins or folic acid (Czeizel 1994; ICMR 2000; MRC 1991); multivitamins with or without folic acid versus folic acid (Kirke 1992; MRC 1991; Zeng 2008); multivitamins with or without vitamin A versus vitamin A or placebo (Fawzi 1998); multivitamins versus control (People's League 1942); multivitamins with vitamin E versus multivitamins without vitamin E or control (Rush 1980); multivitamins with iron and folic acid versus iron and folic acid (Bhutta 2009; Fawzi 2007; Osrin 2005; Roberfroid 2008; Rumiris 2006; Sunawang 2009; Summit 2008; Tofail 2008; West 2014; Zagre 2007).

Primary outcomes

The risk for **total fetal loss** was reduced in women supplemented with:

1. multivitamin without folic acid (RR 0.49, 95% CI 0.34 to 0.70, one trial, 907 women; Analysis 10.1);
2. multivitamin with/without vitamin A (RR 0.60, 95% CI 0.39 to 0.92, one trial, 1074 women; Analysis 15.1);

compared with placebo or no multivitamin groups.

There was no difference in the risk of **total fetal loss** for the following interventions:

1. multivitamin plus iron and folic acid compared iron and folate only groups (RR 0.96, 95% CI 0.93 to 1.00, 10 trials, 94,948 women; Analysis 9.1; *high-quality evidence*);
2. multivitamins alone or in combination with other vitamins or micronutrients compared with placebo or no multivitamins groups (Analysis 11.1; Analysis 12.1; Analysis 13.1; Analysis 14.1; Analysis 16.1; Analysis 17.1; Analysis 18.1 (random effects; three trials)).

Similarly, we found no difference in the risk for **early or late miscarriage** between women receiving the following interventions:

1. multivitamin plus iron and folic acid compared iron and folate only groups (RR 0.98, 95% CI 0.94 to 1.03, 10 trials, 94,948 women; Analysis 9.2; *moderate-quality evidence*);
2. multivitamins alone or in combination with other vitamins or micronutrients compared with placebo or no multivitamins groups (Analysis 10.2; Analysis 11.2; Analysis 12.2; Analysis 13.2; Analysis 14.2; Analysis 17.2; Analysis 18.2 (random effects; three trials)).

The heterogeneity in Analysis 18.1 and Analysis 18.2 seemed to have been contributed by ICMR 2000, which included women who had previously given birth to a child with an open neural tube defect. When this trial was excluded, the heterogeneity was no longer present.

Secondary outcomes

There was evidence of a decrease in the risk for **stillbirth** among women receiving multivitamin plus iron and folic acid compared iron and folate only groups (RR 0.92, 95% CI 0.85 to 0.99, 10 trials, 79,851 women; Analysis 9.3; *high-quality evidence*).

There was no difference in the risk of:

1. **stillbirth** (Analysis 10.3; Analysis 11.3; Analysis 12.3; Analysis 13.3; Analysis 14.3; Analysis 16.2; Analysis 17.3; Analysis 18.3); or
2. **congenital malformation** (Analysis 10.4; Analysis 11.4; Analysis 12.4; Analysis 13.4; Analysis 14.4; Analysis 18.4) between women receiving multivitamins alone or in combination with other vitamins or micronutrients compared with placebo or no multivitamins groups.

There were no data available to conduct any analysis for **adverse effects of vitamin supplementation**.

Folic acid supplementation

The trials involving folic acid supplementation included the following interventions: folic acid with or without multivitamins compared with no folic acid or multivitamins (Czeizel 1994; ICMR 2000; MRC 1991); folic acid with or without multivitamins compared with multivitamins (Kirke 1992; MRC 1991); folic acid and iron compared with iron (Fleming 1968); folic acid and iron compared with no iron or folic acid (Fleming 1986).

Primary outcomes

We found no difference in the risk of:

1. **total fetal loss** (Analysis 19.1 (random effects; three trials); Analysis 20.1; Analysis 21.1; Analysis 22.1; Analysis 23.1; Analysis 24.1; Analysis 25.1; Analysis 26.1); or
2. **early or late miscarriage** (Analysis 19.2 (random effects; three trials); Analysis 20.2; Analysis 21.2; Analysis 22.2; Analysis 23.2; Analysis 24.2; Analysis 25.2; Analysis 26.2);

between women supplemented with folic acid with or without multivitamins and/or iron compared with no folic acid groups. The heterogeneity found seemed to have been contributed by ICMR 2000, which included women who had previously given birth to a child with an open neural tube defect. Excluding this trial removed the heterogeneity but did not change the conclusion of no difference between the treatment groups.

Secondary outcomes

There was no difference in the risk of:

1. **stillbirth** (Analysis 19.3; Analysis 20.3; Analysis 21.3; Analysis 22.3 (random effects); Analysis 23.3; Analysis 24.3 (random effects); Analysis 25.3); or
2. **congenital malformations** (Analysis 19.4; Analysis 20.4; Analysis 21.4; Analysis 22.4 (random effects); Analysis 23.4; Analysis 24.4 (random effects)) between women supplemented with folic acid with or without multivitamins and/or iron;

compared no folic acid groups. There were no data available to conduct any analysis for **adverse effects of vitamin supplementation**.

Antioxidant vitamins supplementation

The trial involving antioxidant vitamins supplementation included the following interventions: antioxidant with multivitamins compared multivitamins with low antioxidant content (Wibowo 2012).

Primary outcomes

In the one trial involving 110 women (Wibowo 2012), there was no evidence of differences between women given antioxidant with multivitamins compared multivitamins with low antioxidant group on **early or late miscarriage** (RR 1.12, 95% CI 0.24 to 5.29, one trial, 110 women, Analysis 27.1). No other primary or secondary outcomes were reported by this trial.

Subgroup analyses by dose of vitamins and duration of vitamin usage

Subgroup analyses by dose of vitamin(s) (below or above the recommended dietary intake) were complicated by the limited number of studies in each vitamin group, and by the use of multivitamin supplements. For many of the vitamin types and for those reporting pregnancy loss outcomes, all of the trials supplemented women with amounts that were above the recommended dietary intake. Similarly, the duration of vitamin usage was complicated by the fact that many of the trials had wide recruitment periods, and one trial (Katz 2000) supplemented women up until three years postpartum. We have not performed subgroup analyses based on vitamin dosage or time of trial entry.

Subgroup analyses by women's risk of spontaneous or recurrent miscarriage

Information enabling women to be classified at high or low risk of either spontaneous miscarriage or recurrent miscarriage was not clearly stated in any of the trials included in this update. Based on the inclusion criteria, one trial (Rumbold 2006) included women at low risk of miscarriage. One trial (Briscoe 1959) included women who had experienced recurrent miscarriage as well as women at high risk of miscarriage (more than two previous miscarriages and/or bleeding in the pregnancy) and low-risk women (two or less previous miscarriages and no bleeding in the pregnancy). After classifying women into these groups, the number of women in the high-risk group was too small to permit any meaningful comparisons and we have therefore not performed subgroup analyses.

Subgroup analyses by dietary intake of vitamins

Seven trials (Bhutta 2009; Fleming 1968; Kumwenda 2002; People's League 1942; Schmidt 2001; Steyn 2003; West 2011) reported information about women's nutritional status or the percentage of women who were dietary deficient at trial entry for the vitamin of interest. Other trials reported that they were being undertaken in countries where the population was at high risk of multiple micronutrient deficiencies (Osrin 2005; Prawirohartono 2011; Roberfroid 2008; Summit 2008; Villar 2009), or there was a high prevalence of anaemia (Bhutta 2009; Fleming 1986; Sunawang 2009; Zagre 2007; Zeng 2008), but provided no specific information on nutritional status of participants. Two trials (Rumiris 2006; Wibowo 2012) included women with 'low antioxidant status'. There were not enough trials within each vitamin group to assess the role of supplementation in women with dietary deficient intakes of the individual vitamins and results were not reported separately for women with a low dietary vitamin intake; therefore, we could not perform subgroup analyses.

Sensitivity analyses

We carried out sensitivity analysis to explore the effects of trial quality and type of randomisation on the primary outcomes related to fetal loss (total fetal loss and early or late miscarriage). We included only trials with 'adequate' rating on allocation concealment, but found that restricting to only trials with adequate allocation concealment made very little difference to the results for the primary outcomes. Effect of type of randomisation was explored by excluding cluster-randomised trials and restricting the analyses to individually-randomised trials. We found no difference between women supplemented with multivitamins compared with controls for total fetal loss or early or late miscarriage when the analyses were restricted to individually-randomised trials only. These sensitivity analyses indicate that the analyses for the effects of multivitamins on outcomes related to fetal loss and early or late miscarriage are no different when only individually-randomised trials are included.

DISCUSSION

Summary of main results

The purpose of this review was to determine the effectiveness and safety of any vitamin supplementation taken by women pre- or periconceptionally on the risk of miscarriage. In this updated version of the review, we included 40 studies involving 59,094 women from individually-randomised trials plus a further 217,726 women from eight cluster-randomised controlled trials. The results did not provide sufficient evidence to support the use of single vitamin supplementation for preventing total fetal loss or early or late miscarriage. However, stillbirth was significantly lower in women given multivitamin supplementation plus iron and folic acid compared to iron and folic acid alone. Although there was evidence of decreased risk for total fetal loss among women receiving multivitamins without folic acid compared with no multivitamin/folic acid and multivitamin supplementation with/without vitamin A compared with vitamin A or placebo; these findings occurred in analyses involving one trial each with small numbers of women involved. Also, they include studies where the comparison groups included women receiving either vitamin A or placebo, and thus require caution in interpretation.

Overall completeness and applicability of evidence

There was considerable consistency in reported total fetal loss (including miscarriages or combined miscarriages and stillbirths) among included studies with no difference in the rates of miscarriage and stillbirth across treatment groups. While this may suggest the true effect of vitamin supplementation on risk of miscarriage, most of the studies included in this review did not originally set out to examine the effect of vitamin supplementation on the risk of miscarriage.

Our review included trials that randomised women prior to conception; however, in some cases, not all women enrolled in these trials fell pregnant during the study period. Some of the trials reported outcomes only for women falling pregnant, whereas other trials did not distinguish between women who were never pregnant and women who may have been pregnant but were lost to follow-up. The outcomes in this review relating to pregnancy outcomes are not relevant for the women who never became pregnant during the study period. In this review, where trials provided accurate information about the number of women who joined the study and became pregnant in the time period, we included this number in the totals, rather than the number of women who may have been randomised. Where it was not clear about the exact number of women with a confirmed pregnancy, we included all women who had been randomised. This may therefore mean that a certain proportion of women in the denominator were never pregnant during the study period. By including these women who were never pregnant in the totals, the review assumes that if these women had become pregnant, they would not have had a miscarriage, which is unlikely to be entirely correct. Including these women creates the potential to underestimate any treatment effects observed.

Similarly, for one large trial (Katz 2000) and one smaller trial (Roberfroid 2008), some women were pregnant more than once during the study period. In these trials, the denominators reported are the total number of pregnancies during the study period, not the total number of women randomised, which incorrectly assumes that each data point included is independent from the next. This has the potential to either underestimate or overestimate the results, depending on whether the women contributing data for more than one pregnancy may be more or less susceptible to experiencing miscarriage or stillbirth. One way to overcome this may be to summarise the data for each woman so that there is only one set of data points for each woman; however, we were unable to do this for these particular studies.

Quality of the evidence

Some of the trials included in the review were at high risk of bias, either due to poor or unclear allocation concealment or large losses to follow-up. The data were also complicated by differing definitions of miscarriage. For some trials, miscarriage was considered to occur up until 26 or 28 weeks' gestation, while other studies reported miscarriage as pregnancy loss prior to 20 weeks' gestation, and stillbirth as pregnancy loss greater or equal to 20 weeks' gestation. Other studies did not specify their definition of miscarriage or stillbirth. In addition to the problems with differing definitions, the timing of the onset of vitamin supplementation for some of the included trials occurred in mid-pregnancy, which may limit the impact of supplementation on the risk of miscarriage. The review attempted to overcome these issues by using the outcome 'total fetal loss', which included either miscarriage or stillbirth.

We assessed the quality of the evidence using GRADE and judged the evidence for vitamin C and vitamin E compared with control as high quality for total fetal loss, and moderate quality for early or late miscarriage, stillbirth, and adverse effects, which was downgraded due to wide 95% confidence intervals (CIs) (Summary of findings for the main comparison). For vitamin A plus iron plus folate versus iron plus folate trials were judged to have low quality of evidence for total fetal loss, early or late miscarriage, and stillbirth due to design limitation and wide 95% CI (Summary of findings 2). No studies reported any adverse effects for this comparison. For multivitamin plus iron plus folate versus iron plus folate trials were judged to be high quality for total fetal death and stillbirth, moderate quality for early or late miscarriage, downgraded due to publication bias suspected by funnel plot, or wide CI crossing the line of no effect (Summary of findings 3). No studies reported any adverse effects for this comparison.

In order to determine the effect of publication bias, we undertook funnel plots for comparisons with 10 or more studies (Figure 3; Figure 4; Figure 5) for the comparisons of multivitamins plus iron and folic acid versus iron and folic acid. Asymmetry was suggested by visual assessment of Figure 4 for early or late miscarriage.

Figure 3. Funnel plot of comparison: 9 Multivitamin plus iron and folic acid versus iron and folic acid, outcome: 9.1 Total fetal loss.

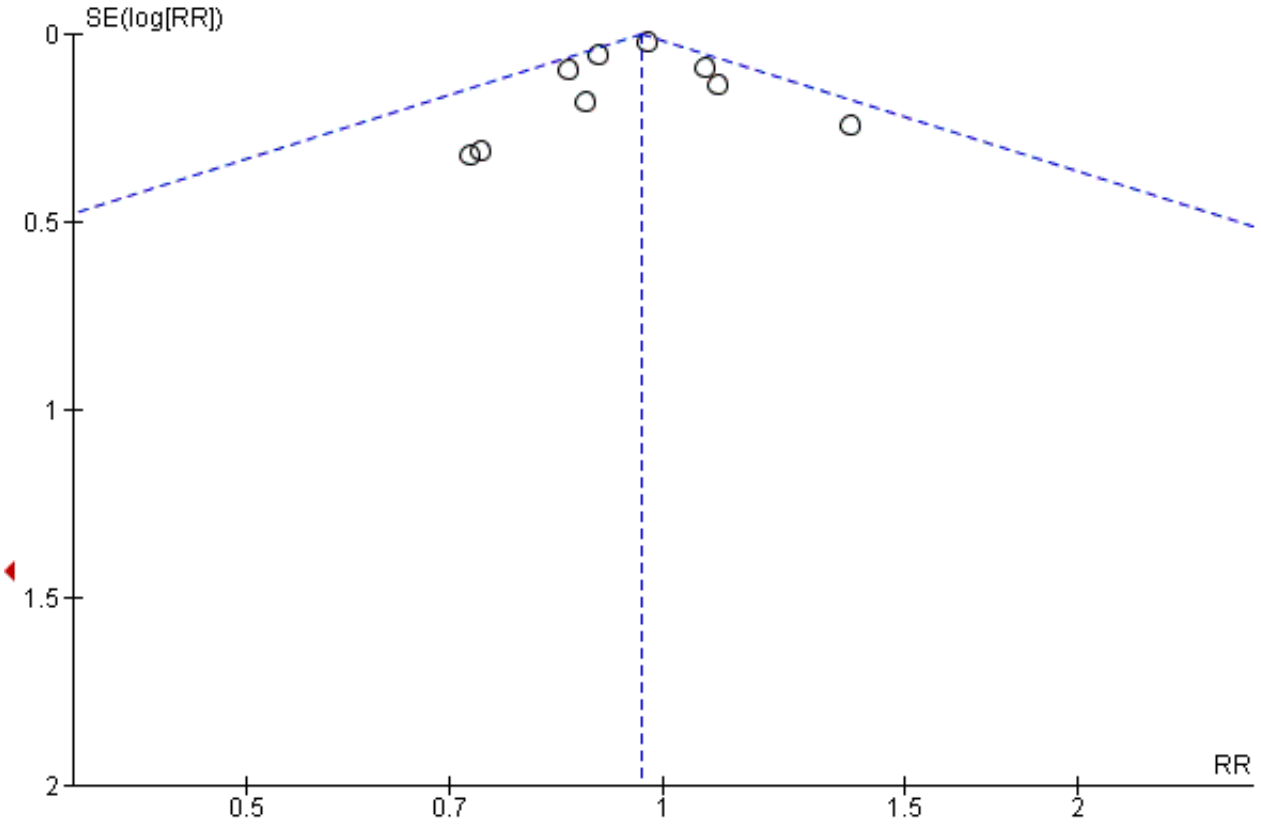


Figure 4. Funnel plot of comparison: 9 Multivitamin plus iron and folic acid versus iron and folic acid, outcome: 9.2 Early or late miscarriage.

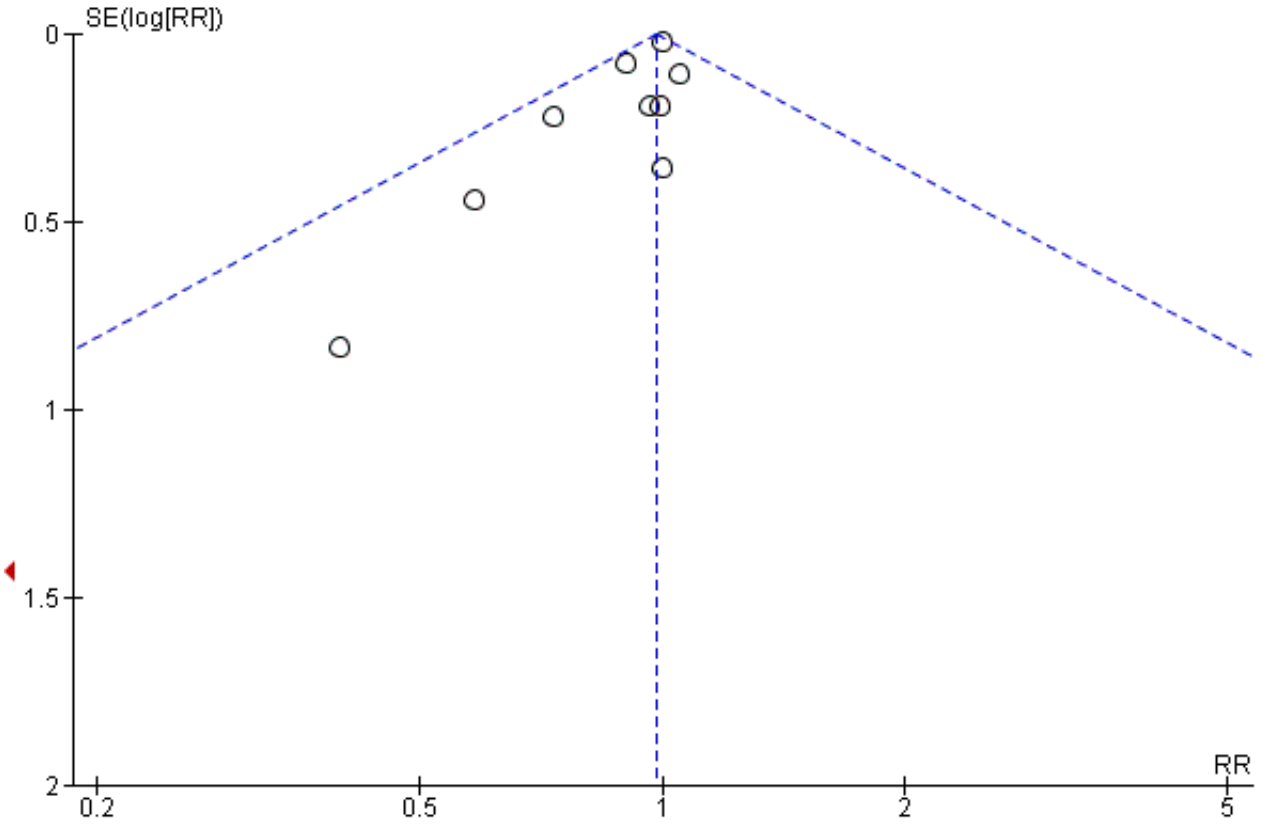
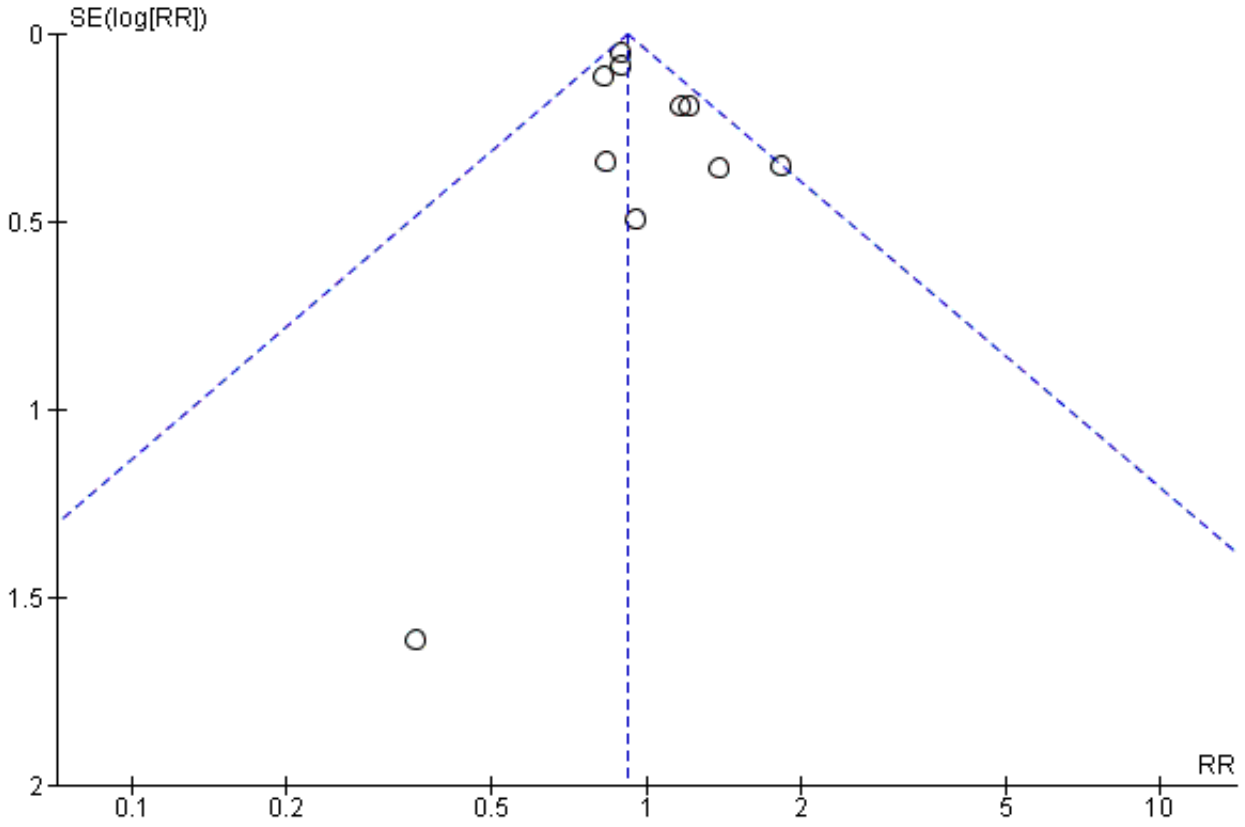


Figure 5. Funnel plot of comparison: 9 Multivitamin plus iron and folic acid versus iron and folic acid, outcome: 9.3 Stillbirth.



Potential biases in the review process

We took steps to minimise the introduction of bias during the review process. All relevant trials were identified including published abstracts from conference proceedings, English and non-English publications. A pro forma translation sheet was used to extract relevant information from non-English articles. At least two review authors independently assessed each trial, performed data extraction, and assessment of risk of bias for each of the included trials. Our assessment of previously identified ongoing trials that remained unpublished were limited to trial published protocols or the records of the initial communication between our authors and the authors of the unpublished trials.

Agreements and disagreements with other studies or reviews

There are several Cochrane reviews evaluating the effect of single vitamin supplementation during pregnancy on maternal, fetal, neonatal and infant outcomes. Benefits or hazards of vitamin supplementation in pregnancy on total fetal loss and miscarriage have not been or insufficiently investigated. However, our results on secondary outcomes are consistent with finding in the particular publications.

In the analysis by vitamin type, vitamin C supplementation alone or in combination with vitamin E or multivitamins did not show any effect on total fetal loss, miscarriage, or the secondary outcomes stillbirth, congenital malformation and adverse effects. A review focusing on vitamin C supplementation alone or in combination with other separate supplements on pregnancy outcomes, did not observe effects on stillbirth or congenital malformations which is consistent with our results (Rumbold 2015).

Supplementing women with vitamin A alone or in combination with iron and folic acid or multivitamins was not associated with changes in fetal loss or miscarriage as well as stillbirth. These findings are consistent with the Cochrane review '*Vitamin A supplementation during pregnancy for maternal and newborn outcomes*' (McCauley 2015), which found no difference in the rate of stillbirth for women receiving vitamin A alone compared with placebo/no treatment or vitamin A with other micronutrients compared with micronutrient supplementation without vitamin A.

In the analysis comparing multivitamin alone or in combination with other vitamins, we found a positive effect of multivitamin supplementation without folic acid compared with no multivitamin/folic acid as well as multivitamin with/without vitamin A compared with vitamin A alone or placebo on total fetal loss. However, these findings resulted from only one study, respectively. Stillbirth was significantly reduced for women receiving multivitamin plus iron and folic acid. This result is consistent with findings in a review assessing the effect of multiple-micronutrient supplementation during pregnancy on maternal, fetal and infant health outcomes (Haider 2015). Here they also reported a significant reduction in the risk of stillbirth. Miscarriage (loss before 28 weeks) was not effected by this intervention.

Folic acid supplementation with or without multivitamin compared to no folic acid/multivitamin or multivitamin alone did not reduce the risk of total fetal loss, miscarriage, stillbirth or congenital malformations. This in accordance with a review evaluating the effectiveness of oral folic acid supplementation during pregnancy on maternal health and pregnancy outcomes (Lassi 2013). The authors did not observe any effect of folic acid supplementation on stillbirth. Even though miscarriage was included as a secondary outcome, none of the included studies reported on miscarriage. In addition, another review assessed the effects and safety of periconceptional oral folate supplementation for preventing birth defects (De-Regil 2015). There was no effect of folate versus no intervention, placebo or other micronutrients without folate on miscarriage or stillbirth. They investigated the effect of folate supplementation on several congenital malformations and found a 69% reduction in the risk of neural tube defects.

Antioxidant vitamin supplementation had no effect on early or late miscarriage. The effectiveness and safety of any antioxidant supplementation during pregnancy on the risk of various pregnancy outcomes is explored in the Cochrane review '*Antioxidants for preventing pre-eclampsia*' (Rumbold 2008). Our results are in accordance with the results form this review where any antioxidant supplementation compared to control or placebo had no effect on miscarriage or stillbirth.

AUTHORS' CONCLUSIONS

Implications for practice

There is no evidence to support the prophylactic use of single vitamins to prevent either early or late miscarriages. Supplementing women with multivitamin with or without iron and/or folic acid or vitamin A, may decrease the risk of total fetal loss and stillbirth, Even though there is a positive effect of multivitamin supplementation on pregnancy outcomes, there was insufficient evidence to examine the effect of different combinations of vitamins on miscarriage and miscarriage-related outcomes. Our findings suggest, that no particular vitamin decreases the risk of miscarriage or stillbirth, but the combination of various vitamins may have the potential to positively influence pregnancy outcomes. This could be due to an overall improvement in maternal nutrition and health status, making women more resistant to infections during pregnancy. However, this needs to be investigated further before recommendations on routine multivitamin supplementation to prevent miscarriage can be given.

Implications for research

The impact of different combinations of vitamins (i.e. individual vitamins or multivitamin preparations with or without vitamin A and folic acid) on miscarriage and miscarriage-related outcomes is unclear. Any future studies of vitamin supplementation should be high quality and focus on women at high risk of miscarriage. Considerations should include timing of the intervention and trials should assess the most appropriate vitamin type and dosage; to see whether it is beneficial without causing any harms to the mother or fetus and include assessments of any psychological effects and long-term follow-up of mothers and infants. Further, the data in the current review were complicated by differing definitions of miscarriage and so this may be an important issue to consider in any future trials.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Bhutta 2009

Methods	Randomisation and allocation concealment: random allocation of the entire population of the urban and rural areas (population, 110,000; 20,400 households) into 28 discrete clusters (16 rural and 12 urban) on the basis of household characteristics, socioeconomic criteria, and geographic location. Each cluster was allocated to a community health worker who distributed the supplements on a cluster-based allocation strategy of supplements ("either iron–folic acid or multiple micronutrients"). Distribution of the sealed, coded supplement bottles were independently controlled by the pharmacy at Aga Khan University. Blinding of outcome assessment: medical officers, community health workers, social scientists, and data collection team remained blinded to the supplementation allocation. Documentation of exclusion: 373 women (16.5%) were excluded. Use of placebo control: no placebo given, women in the control group were given IFA.
Participants	2378 women from community settings in urban and rural Sindh (Pakistan) less than 16 weeks of gestation. Eligible women were women with a confirmed pregnancy at less than 16 weeks of gestation. Women who did not have a confirmed pregnancy on ultrasound scanning or women who were clearly advanced beyond 24 weeks of gestation were excluded.
Interventions	Multiple micronutrients comprised 30 mg of iron (ferrous fumarate) and 400 mcg of folic acid along with 800 mcg of retinol (retinyl acetate), 200 IU of vitamin D (ergocalciferol), 10 mg of vitamin E (α-tocopherol acetate), 70 mg of ascorbic acid, 1.4 mg of vitamin B1 (thiamine mononitrate), 18 mg of niacin (niacinamide) 1.4 mg of vitamin B2, 1.9 mg of vitamin B6 (pyridoxine), 2.6 mcg of vitamin B12 (cyanocobalamin), 15 mg of zinc (zinc gluconate), 2 mg of copper, 65 mcg of selenium, and 150 mcg of iodine. Intervention was timed to start at less than 16 weeks' gestation. Comparison was iron (60 mg) and folic acid (400 mcg).
Outcomes	Maternal outcomes: 1. Blood Hb level as well as serum ferritin, zinc, and vitamin A. 2. Physical and clinical examination, including a morbidity assessment and measurement of fundal height. 3. Height, weight, and mid-upper-arm circumference. Infant outcomes: 1. Birthweight.

Bhutta 2009 *(Continued)*

2. Gestational age.
3. Neonatal death and cause of death.

Notes	Women's risk of spontaneous and recurrent miscarriage is unclear. Womens' BMI, Hb, ferritin, zinc, and serum retinol at admission are reported. Sample-size calculation reported by 2 methods: 1. based on a potential 5% gain in birthweight, 2. based to estimate a difference in birthweight of 150 g between the 2 groups. No intention-to-treat analyses performed. Compliance: community health worker performed a tablet count every fourth nightly visit. Proportion of tablets consumed 75.65 in the intervention group and 76.7% in the control group. Location: urban population (Bilal Colony, Karachi) and rural villages (Kot Diji district, rural Sindh), Pakistan. Timeframe: unclear.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"We randomly allocated the entire population of the urban and rural area." Pg S497.
Allocation concealment (selection bias)	Low risk	"cluster-based allocation strategy of supplements (either iron–folic acid or multiple micronutrients) by the community health workers was implemented. The allocation of either iron–folic acid or multiple micronutrient supplements and the distribution of the sealed, coded supplement bottles were independently controlled by the pharmacy at Aga Khan University, which maintained the allocation codes by individual community health workers." Pg S498.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	All pregnant women were allocated a unique code and a uniquely labelled and numerically coded specific supplement supply for the duration of pregnancy. Blinding is unlikely to have been broken. Pg S498.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"The field staff (medical officers, community health workers, social scientists, and data collection team) remained completely blinded as to the supplement allocation." Pg S498.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Approximately 16.5% of attrition with balanced number and similar reason for each group. S500 Figure1.
Selective reporting (reporting bias)	Unclear risk	No information about trial registration.
Other bias	High risk	The distribution of study participants across the urban and rural areas is unclear from the text and no adjustments were made for cluster design.

Briscoe 1959

Methods	Randomisation and allocation concealment: unclear, no methodological details given, dubious as the number of women allocated to the treatment group was more than double that allocated to the place-

Briscoe 1959 *(Continued)*

	bo group. "Unselected patients were each given 200 capsules... these were given a code, unknown to us and contained either an inert powder or 100 mg each of ascorbic acid and hesperidin." Blinding of outcome assessment: women and study investigators did not know the treatment codes. Documentation of exclusion: none reported. Use of placebo control: placebo given; however, all women received an additional multivitamin supplement.
Participants	406 women were recruited in the study. Eligible women were "unselected patients" in private obstetrics care, who were less than or equal to 10 weeks' pregnant, and were eligible regardless of whether they were currently bleeding or the number of previous pregnancies. Women greater than 10 weeks' gestation were excluded. 406 women were randomised to either vitamin C (n = 303) or placebo (n = 103), no losses to follow-up were reported. 77 women in the study had more than 2 previous miscarriages and/or bleeding in the pregnancy, and 329 had 2 or fewer miscarriages and no bleeding in the pregnancy.
Interventions	All women were given 200 tablets, containing either 100 mg each of ascorbic acid and hesperidin or placebo (an inert powder). The study lasted for 7 weeks. For the first 2 weeks, women were asked to take 8 tablets daily (i.e. daily 800 mg each of vitamin C and hesperidin or placebo). For the following 5 weeks, women took 4 tablets daily (i.e. daily 400 mg each of vitamin C and hesperidin or placebo). All women received a multiple vitamin supplement containing 50 mg vitamin C.
Outcomes	1. Spontaneous miscarriage. 2. Spontaneous miscarriage in women with 2 or fewer previous miscarriages and no bleeding in the current pregnancy. 3. Spontaneous miscarriage in women with more than 2 previous miscarriages and/or bleeding in the current pregnancy. 4. Spontaneous miscarriage in women who experienced recurrent miscarriage.
Notes	Women's risk of spontaneous and recurrent miscarriage is unclear, as there is no information about concurrent medical conditions or other risk factors for miscarriage. 9 of the 406 women were classified as experiencing recurrent miscarriage. No information is available about women's nutritional status. No sample-size calculation reported. Intention-to-treat analyses performed (no losses to follow-up reported). Compliance: no compliance information reported. Location: Philadelphia, USA. Timeframe: unclear.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No methodological details given.
Allocation concealment (selection bias)	Unclear risk	No methodological details given.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Women and study investigators did not know the treatment allocation.
Blinding of outcome assessment (detection bias)	Unclear risk	Double-blind study, but it is unclear who was blinded and if the code was broken before or after outcome assessment pg289.

Briscoe 1959 *(Continued)*
All outcomes

Incomplete outcome data (attrition bias) All outcomes	Low risk	No losses to follow-up reported.
Selective reporting (reporting bias)	Unclear risk	Limited information about selection bias, stated that 'unselected patients' were included.
Other bias	Unclear risk	Limited methodological details provided including patient compliance.

Chappell 1999

Methods	Randomisation and allocation concealment: a computer-generated randomisation list using blocks of 10 was given to the hospital pharmacy departments. Researchers allocated the next available number to participants and women collected the trial tablets from the pharmacy department. Blinding of outcome assessment: women, caregivers and researchers were blinded to the treatment allocation until recruitment, data collection and laboratory analyses were complete. Documentation of exclusion: 123 (43.5%) women were excluded, of which 70 women were withdrawn because their second Doppler scan was normal. Pregnancy outcome data were reported for all women randomised. Use of placebo control: placebo control.
Participants	283 women were recruited into the study. Inclusion criteria: abnormal Doppler waveform in either uterine artery at 18-22 weeks' gestation or a history in the preceding pregnancy of pre-eclampsia necessitating delivery before 37 weeks' gestation, eclampsia or the syndrome of HELLP. Exclusion criteria: heparin or warfarin treatment, abnormal fetal-anomaly scan or multiple pregnancy. Women were randomised at 18-22 weeks' gestation; however, women with a previous history who were identified at an earlier stage were randomised at 16 weeks' gestation. Women with abnormal Doppler waveform analysis returned for a second scan at 24 weeks' gestation, those with a normal waveform at this time stopped treatment and were withdrawn from the study. The remaining women who had persistently abnormal waveforms, and those with a previous history or pre-eclampsia remained in the study and were seen every 4 weeks through the rest of pregnancy. 1512 women underwent Doppler screening, 273 women had abnormal waveforms and of these, 242 women consented to the study. An additional 41 women who had a history of pre-eclampsia consented. 283 women were randomised to either the vitamin C and E group (n = 141) or the placebo group (n = 142), 72 women had normal Doppler scans at 24 weeks' gestation and 24 women did not return for a second scan and were withdrawn. A further 27 women withdrew from the trial after 24 weeks' gestation for various reasons. In total, 160 women completed the trial protocol until delivery, 79 in the vitamin C and E group and 81 in the placebo group. Pregnancy outcome data were presented for all women randomised (n = 283) as well as only for those women completing the trial protocol (n = 160).
Interventions	Women randomised to the vitamin C and E group received tablets containing 1000 mg vitamin C daily and capsules containing 400 IU vitamin E daily. Women randomised to the placebo group received tablets containing microcrystalline cellulose and soyabean oil, that were identical in appearance to the vitamin C tablets and vitamin E capsules. After 24 weeks' gestation women were seen every 4 weeks, and blood samples were taken at each visit.
Outcomes	1. Ratio of PAI-1 to PAI-2. 2. Incidence of pre-eclampsia. 3. Placental abruption. 4. Spontaneous preterm delivery (< 37 weeks). 5. Intrauterine death. 6. Small-for-gestational-age infants (on or below the 10th centile).

Chappell 1999 *(Continued)*

7. Mean systolic and diastolic blood pressure before delivery.
8. Gestational age at delivery (median, IQR).
9. Birthweight (median, IQR).
10. Birthweight centile (median, IQR).

Notes	Women's risk of spontaneous and recurrent miscarriage is unclear, women were at high risk of pre-eclampsia. No information is available about women's nutritional status. Sample-size calculation reported, based on a 30% reduction in PAI-1. Intention-to-treat analyses performed. Compliance: "within the treated group, plasma ascorbic acid concentration increased by 32% from baseline values and plasma alpha-tocopherol increased by 54%". Location: London, UK. Timeframe: unclear.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated random number list.
Allocation concealment (selection bias)	Low risk	Random number list used blocks of 10 and was held by the pharmacy department.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Women, caregivers and researchers were blinded until the analyses were completed.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"The code was revealed to the researchers once recruitment, data collection, and laboratory analyses were complete" pg811.
Incomplete outcome data (attrition bias) All outcomes	Low risk	123 (43.5%) women were excluded, of which, 70 women were withdrawn because their second Doppler scan was normal. Data were reported for all women randomised.
Selective reporting (reporting bias)	Low risk	Data reported for all outcomes in methods.
Other bias	Low risk	The study appears to be free of other sources of bias.

Czeizel 1994

Methods	Randomisation and allocation concealment: unclear, "women agreed to their allocation on the basis of a random table". Blinding of outcome assessment: unclear, women were aware of the "blind use of one of two kinds of tablets", but no other details given. Documentation of exclusion: 49 women (1%) were lost to follow-up and excluded. Use of placebo control: "trace element control" given.
Participants	7765 women were recruited into the study. Women participating in the HOFPP who volunteered to take part, were not currently pregnant, and who conceived within 12 months of ceasing contraception. In

Czeizel 1994 *(Continued)*

	the first 2 years of the HOFPP, women were also required to be aged < 35 years, and not to have had a previous pregnancy except a prior induced abortion. 7905 women were approached, of which 140 refused participation, 7765 were randomised and 5502 women had a confirmed pregnancy and were allocated to either multivitamins (n = 2819) or control (n = 2683). 49 women of the 5502 confirmed pregnancies were lost to follow-up.
Interventions	Women were provided with multivitamin or trace element 'control' from at least 28 days before conception continuing until at least the second missed menstrual period. The multivitamin with folic acid contained 6000 IU vitamin A, 1.6 mg vitamin B1, 1.8 mg vitamin B2, 2.6 mg vitamin B6, 4.0 mcg vitamin B12, 100 mg vitamin C, 500 IU vitamin D, 15 mg vitamin E, 19 mg nicotinamide, 10 mg calcium pantothenate, 0.2 mg biotin, 0.8 mg folic acid, 125 mg calcium, 125 mg phosphorus, 100 mg magnesium, 60 mg iron, 1 mg copper, 1 mg manganese, 7.5 mg zinc. The trace element control contained 7.5 mg vitamin C, 1 mg copper, 1 mg manganese and 7.5 mg zinc.
Outcomes	1. NTDs and other birth defects. 2. Miscarriage. 3. Ectopic pregnancy. 4. Termination of pregnancy. 5. Live births. 6. Stillbirths. 7. Multiple gestation. 8. Subgroup data are available on menstrual cycle, first trimester symptoms and sexual activity.
Notes	Women's risk of spontaneous and recurrent miscarriage is unclear. Information on their dietary status is unknown. No sample-size calculation reported. Partial intention-to-treat analyses performed. Compliance: compliance was assessed by questioning, checking the tick-off on the basal temperature chart and counting of unused tablets. 70% of women in the multivitamin group and 71% in the control group took the full course of the supplements, with an additional 20% and 21% in the multivitamin and control groups respectively receiving a partial course of supplementation. Location: Hungary. Time frame: 1 February 1984 to 30 April 1992. The denominators used for this trial are the number of women randomised and with a confirmed pregnancy (i.e. 2819 for the multivitamin group and 2683 for the control group).

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Methodological details unclear.
Allocation concealment (selection bias)	Unclear risk	Methodological details unclear, 'women agreed to their allocation on the basis of a random table'.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Women were aware of the 'blind use of one of two kinds of tablets', but no other details given.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No details are given if outcome assessment was blinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	49 women (1%) excluded, partial intention-to-treat analyses performed.

Czeizel 1994 *(Continued)*

Selective reporting (reporting bias)	Unclear risk	Denominators vary with serial publications.
Other bias	Unclear risk	Limited methodological details provided.

Fawzi 1998

Methods	Randomisation and allocation concealment: block randomisation using blocks of 20, eligible women were "assigned the next numbered bottle of regimen". The study used a 2 by 2 factorial design and women were randomised to 1 of 4 groups. Tablets were indistinguishable and packaged in identically coded bottles. Blinding of outcome assessment: women and study investigators were unaware of the treatment allocation, no information given about blinding of outcome assessors. Documentation of exclusion: 64 women (6%) were lost to follow-up and excluded. Use of placebo control: placebo given.
Participants	1085 women were recruited into the study. Pregnant women between 12 and 27 weeks' gestation who were HIV-1 infected, living in Dar es Salaam and intended to stay there for at least 1 year were eligible for the study. Women not HIV-1 positive or moving out of Dar es Salaam were excluded. 13,879 pregnant women consented to be HIV-1 tested, of which 1806 were positive, and 1085 were randomised. Of these, 3 women were not pregnant and 7 women died before delivery and were excluded from the trial. Of the remaining 1075 women, 54 women (5%) were lost to follow-up by the time of delivery, leaving birth outcomes reported for 1021 women. Women were randomised to 1 of 4 groups: vitamin A (n = 269), multivitamins excluding vitamin A (n = 269); multivitamins including vitamin A (n = 270) or placebo (n = 267).
Interventions	Women were randomised to 1 of 4 groups: 1. vitamin A (30 mg beta-carotene plus 5000 IU preformed vitamin A); 2. multivitamins excluding vitamin A (20 mg vitamin B1, 20 mg vitamin B2, 25 mg vitamin B6, 100 mg niacin, 50 mcg vitamin B12, 500 mg vitamin C, 30 mg vitamin E, 0.8 mg folic acid); 3. multivitamins including vitamin A, all formulated in 2 tablets; or 4. placebo. All women received 400 mg ferrous sulphate and 5 mg folic acid daily, as well as 500 mg chloroquine phosphate weekly. At delivery, all women taking vitamin A were to receive an additional oral dose of 200,000 IU vitamin A and the others an extra dose of a placebo. Pill counts were conducted at each visit and new tablets were given out at each visit.
Outcomes	1. Miscarriage, defined as delivery before 28 weeks' gestation. 2. Stillbirth, defined as delivery of a dead baby at or after 28 weeks' gestation. 3. Fetal death, defined as either miscarriage or stillbirth. 4. Low birthweight, defined as birthweight less than 2500 g. 5. Very low birthweight, defined as birthweight less than 2000 g. 6. Preterm delivery, defined as delivery before 37 weeks. 7. Severe preterm birth, defined as delivery before 34 weeks. 8. Small-for-gestational age, defined as birthweight less than the 10th percentile for gestational age.
Notes	Women's risk of spontaneous and recurrent miscarriage was unclear, although may be increased due to their HIV-1 positive status. Women's nutritional status is also unclear.

Fawzi 1998 *(Continued)*

Figures change with serial publications, particularly for secondary outcomes, and results are not reported separately for the individual 4 groups. Results are reported as: any multivitamins, multivitamin, any vitamin A or no vitamin A.
Sample-size calculation performed allowing for 20% loss to follow-up.
Intention-to-treat analyses performed.
Compliance: compliance assessed by the percentage of prescribed tablets absent from the returned bottles, and in plasma vitamin A concentrations in a subset of 100 women. Median compliance assessed using pill counts was 90% by the time of delivery.
Location: Tanzania.
Timeframe: April 1995 to July 1997.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Block randomisation using blocks of 20.
Allocation concealment (selection bias)	Unclear risk	Women assigned the 'next numbered bottle of regimen'.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Women and investigators were blinded.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Double-blinded study, but unclear if ocutome assessors were blinded.
Incomplete outcome data (attrition bias) All outcomes	High risk	64 women (6%) were lost to follow-up and excluded, intention-to-treat analyses performed.
Selective reporting (reporting bias)	Unclear risk	Figures change with serial publications, particularly for secondary outcomes, and results are not reported separately for the individual 4 groups.
Other bias	Unclear risk	Limited methodological details provided.

Fawzi 2007

Methods	Randomisation: unclear about sequence generation. Allocation concealment: states a list was prepared according to the randomisation sequence in blocks of 20, tablets were bottled in identical coded bottles, eligible women were given the next numbered bottle. Blinding of outcome assessment: women and research assistants who assessed the study outcomes were unaware of the intervention groups. Documentation of exclusion: 49 women lost to follow-up (multivitamin group: 23, placebo group: 26), no post-randomisation exclusions. Use of placebo control: placebo given.
Participants	8428 women were randomised in the study. Pregnant women between 12 and 27 weeks who had a negative test for HIV infection and planned to stay in the city until delivery and for 1 year thereafter recruited through antenatal clinics in Dar es Salaam. 8468 women were enrolled, however 40 women were

Fawzi 2007 *(Continued)*

	then found to be ineligible. 8428 women were randomly assigned to receive either a multivitamin (n = 4214) or placebo (n = 4214) from the time of enrolment until 6 weeks after delivery. 6 women died before delivery and 43 were lost to follow-up by the time of delivery.
Interventions	The supplements included 20 mg of vitamin B1, 20 mg of vitamin B2, 25 mg of vitamin B6, 100 mg of niacin, 50 mcg of vitamin B12, 500 mg of vitamin C, 30 mg of vitamin E, and 0.8 mg of folic acid. The active tablets and placebo were similar in shape, size, and colour. All women, irrespective of the assigned study regimen, were given daily doses of iron (60 mg of elemental iron) and folic acid (0.25 mg). They were also given malaria prophylaxis in the form of sulfadoxine-pyrimethamine tablets at 20 weeks and 30 weeks of gestation.
Outcomes	1. Low birthweight (< 2500 g). 2. Preterm delivery (before 37 weeks' gestation). 3. Fetal death. 4. Birthweight below 2000 g. 5. Extremely preterm delivery (before 34 weeks). 6. Small-for-gestational age (birthweight below the 10th percentile for gestational age). 7. Fetal death and death in the first 6 weeks of life.
Notes	Women's risk of spontaneous and recurrent miscarriage was unclear. Women's nutritional status is also unclear. Intention-to-treat analyses performed. Compliance: average compliance was 88%, no difference in compliances between the 2 groups. Location: Tanzania. Timeframe: August 2001 and July 2004.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Generation of sequence not reported, except that there were blocks of 20 in the sequence.
Allocation concealment (selection bias)	Low risk	Identical coded bottles prepared according to the randomisation list, eligible women were assigned the next numbered bottle.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Women and outcome assessors were blinded to allocation.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"Research assistants who assessed the study outcomes were unaware of the intervention groups." pg1424.
Incomplete outcome data (attrition bias) All outcomes	Low risk	49 (1%) women lost to follow-up, balanced across groups, analyses by intention-to-treat.
Selective reporting (reporting bias)	Low risk	All pre-specified outcomes appear to be reported.

Fawzi 2007 *(Continued)*

Other bias	Low risk	The study appears to be free of other sources of bias.

Fleming 1968

Methods	Randomisation and allocation concealment: quasi-randomised, alternate women were allocated to receive folic acid or placebo according to the order in which they attended antenatal clinic. No other methodological details were given. Blinding of outcome assessment: women and investigators were blinded to the treatment allocation, until after the completion of the trial. Documentation of exclusion: 21 women (28%) excluded from the analysis. Use of placebo control: control tablet containing iron given.
Participants	75 women were recruited into the trial. Women were eligible if they were primigravida, less than 26 weeks' pregnant (range of gestation 10 to 26 weeks'), with haematocrit value (PCV) 27% or more, and who had not received treatment so far as was known. Women with Hb SC, Hb SS, Hb CC were excluded. Alternate patients were allocated to group A (placebo) or B (folic acid). 75 women were included (40 in group A and 35 in group B) initially; however, only 26 in group A and 28 in group B completed the trial. 16 women (10 in group A and 8 in group B) defaulted from the trial, 3 (2 in group A and 1 in group B) were anaemic on the second visit warranting folic acid treatment, 1 in group A self-medicated with folic acid and 1 in group A 'aborted'.
Interventions	All women received antimalarials and iron supplements as per the standard antenatal care at the hospital. Women in group B received 5 mg folic acid tablets on each attendance, which was fortnightly initially and weekly in the last trimester. Group A received "one tablet of lactose base and colouring matter in the same manner".
Outcomes	1. PCV and reticulocyte index. 2. Serum folic acid concentration and 'megaloblastic score'. 3. Malarial infection. 4. Maternal morbidity (pyelonephritis, pre-eclamptic toxaemia, septicaemia, puerperal psychosis). 5. Prematurity. 6. Birthweight (mean birthweight but no standard deviation). 7. Fetal mortality.
Notes	Results not reported as intention-to-treat; however, where possible, the review authors included data in the review as intention-to-treat. Unclear of women's risk of spontaneous and recurrent miscarriage. 16 women in the trial showed evidence of folic acid deficiency at trial entry. Sample-size calculation: none reported. No intention-to-treat analyses performed. Compliance: no compliance information reported specifically; however, women were "seen to swallow" the tablets at their fortnightly and weekly visits. Location: Nigeria. Time frame: unclear.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Quasi-randomised, alternate allocation.

Fleming 1968 *(Continued)*

Allocation concealment (selection bias)	High risk	Quasi-randomised, alternate allocation.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Women and investigators blinded.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"The identity of the tablets was not known to investigators until after the completion of the trial." pg426.
Incomplete outcome data (attrition bias) All outcomes	High risk	21 women (28%) excluded from the analysis.
Selective reporting (reporting bias)	Unclear risk	Results not reported as intention to treat; however, where possible, the review authors included data in the review as intention to treat.
Other bias	Unclear risk	Limited methodological details provided.

Fleming 1986

Methods	Randomisation and allocation concealment: women were "randomly allocated to one of five groups using a random number table", no other details given. Blinding of outcome assessment: women and investigators were blinded to the treatment allocation, until after the completion of the trial. Documentation of exclusion: 18 women (9%) were excluded due to anaemia at enrolment, 'defaulting', or being 'mentally subnormal', these women were replaced by other women chosen by an investigator. A further 42 women were excluded before delivery and another 30 failed to attend the postnatal clinic, birth outcomes were available for 160 women (80%). Use of placebo control: no placebo control.
Participants	228 women met the eligibility criteria; however 200 pregnant women were recruited into the study. Women were allocated to 1 of 5 groups; 40 women were allocated to each group. Eligible women included: 1. Hausa women living in Zaria and planning to deliver in Zaria; 2. pregnant for the first time; 3. at less than 24 weeks' gestation, as estimated by the height of the fundus uteri; 4. the wives of unskilled or semiskilled men. Women were excluded if they had already taken any antimalarial treatment or haematinics during the pregnancy, or had the following complications: hydatiform mole, Hb SC disease, overt anaemia or proteinuria. The mean gestational age of women at enrolment was 18.5 weeks.
Interventions	Women were allocated to 1 of 5 groups: • group 1: no active treatment (control); • group 2: antimalarials only (600 mg chloroquine/day + 100 mg proguanil/day); • group 3: iron + antimalarials (60 mg iron/day + 600 mg chloroquine/day + 100 mg proguanil/day);

Fleming 1986 *(Continued)*

- group 4: folic acid + antimalarials (1 mg folic acid/day + 600 mg chloroquine/day + 100 mg proguanil/day);
- group 5: iron + folic acid + antimalarials (1 mg folic acid/day + 60 mg iron/day + 600 mg chloroquine/day + 100 mg proguanil/day).

Outcomes	Maternal outcomes 1. Anaemia (severe and mild/moderate) before 28 weeks', between 28-36 weeks', and after 36 weeks' gestation. 2. Gestation age. 3. Mode of delivery. 4. Complications of pregnancy (abortion, hypertension, pre-eclampsia or eclampsia, hydramnios, abdominal pain). Infant outcomes 1. Fetal distress. 2. Birthweight. 3. Apgar score at 2 minutes. 4. Fetal complications. Laboratory outcomes 1. Hb concentration, red cell indices and WBC at first attendance, 28 weeks, 36 weeks, at delivery (form mother and infant) and 6 weeks postpartum. Not all outcomes were reported for each individual treatment group. Miscarriage was reported for the combined groups 4 and 5, therefore for the purpose of this review the groups 4 and 5 are combined (folic acid + iron) and compared with group 2 and group 3 (iron + antimalarials). The authors reported that 8 women had hypertension without other signs, 21 women had pre-eclampsia and 6 developed eclampsia, with no association between these outcomes and treatment group. No other details were provided, including the breakdown of these outcomes by treatment group.
Notes	Women's risk of spontaneous and recurrent miscarriage was unclear. Women were at high risk of anaemia. Information about other nutritional indices was not provided. Intention-to-treat analyses not performed, however, where possible, the review authors included data in the review as intention-to-treat. Compliance: 72 women (36%) were classed as defaulters. Location: Nigeria. Timeframe: unclear.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	A random number table was used but no details provided of how it was generated.
Allocation concealment (selection bias)	Unclear risk	No details provided about the allocation.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Neither the researchers nor the patients were aware of the treatment allocation until after the completion of the study.

Fleming 1986 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Low risk	"Neither the researchers nor the patients were aware of the treatment allocation until after the completion of the study." pg 214.
Incomplete outcome data (attrition bias) All outcomes	High risk	228 women met the entry criteria, but only 200 were included in the trial. 18 women were excluded and replaced by other women.
Selective reporting (reporting bias)	High risk	Not all outcomes are reported by treatment group. In serial publications up to 70% of the data were excluded.
Other bias	Unclear risk	Limited methodological details provided.

Hans 2010

Methods	Randomisation and allocation concealment: women were randomly assigned to receive either 400 mg of vitamin C daily or not in addition to their standard antenatal vitamin. Randomisation was obtained by a computer-generated, block design sequence to receive vitamin C or not in a 1:1 ratio. No other methodological details given. Blinding of outcome assessment: unclear, no details given. Documentation of exclusion: 16 women (4%) did not complete the trial after randomisation. Use of placebo control: no placebo control.
Participants	400 women 4 to 12 gestational weeks of pregnancy confirmed serologically by B-HCG reagent test along with referred last menstrual period not exceeding the past 3 months, aged at least 18. Women with referred pregnancy of more than 3 months by last menstrual period, concomitant HIV infection status, active or recent (< 2 weeks) sexually transmitted disease infection, medical record of any severe organ disease such as heart, liver or renal failure at the time of assessment, diagnosis of pregnancy during inpatient admission for any other reason, recent history of multivitamin supplementation (< 12 weeks) for any reason, except for pregnancy, and patients incapable to read and write.
Interventions	Chewable tablet of synthetic form of L-ascorbic acid or vitamin C 400 mg administered daily 2 tablet 2 times a day, from first trimester until delivery. Comparison received no vitamin C in addition to their standard antenatal vitamin. All women received ferrous sulphate 200 mg, folic acid 5 mg and vitamin B-complex 60 mg once daily tablets. Nutritional counselling was provided to all women.
Outcomes	1. Prevention of hospitalisations during pregnancy. 2. Overall hospitalisations rate. 3. Weight gain during pregnancy (normal < 16 kg). 4. Term pregnancy (≥ 37 gestational weeks). 5. Preterm delivery. 6. miscarriage (< 24 gestational weeks). 7. Low birthweight (< 2500 g). 8. Gestational systolic blood pressure.
Notes	Women's risk of spontaneous or recurrent miscarriage is unclear, as is their dietary intake. Sample-size calculation based on at least 30% of women not hospitalised during pregnancy in the control group and at least 50% of women not hospitalised in the intervention group. Analyses were not based on intention-to-treat.

Hans 2010 *(Continued)*

	Compliance: no details of any compliance assessments were given. Location: Kyeibuza, Uganda. Timeframe: August 2007 and January 2009.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Patients presented to the health centre, those who met the inclusion criteria were randomly assigned...randomization was obtained by a computer-generated, block design sequence to receive vitamin C or not in a 1:1 ratio." pg 3.
Allocation concealment (selection bias)	Unclear risk	No description for allocation concealment in the text. Probably not done.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No information on participant or personnel blinding provided.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No information on outcome assessor blinding provided.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Drop-out rates for each group were not clearly described and no information was provided on the reason of exclusion and attrition.
Selective reporting (reporting bias)	Unclear risk	Although expected outcomes were reported, the study protocol was not available to see if all prespecified outcomes were reported as planned.
Other bias	Low risk	The study appears to be free of other sources of bias.

Hemmi 2003

Methods	Randomisation and allocation concealment: unclear, "patients were randomly assigned to the control group or the study group". No other methodological details given. Blinding of outcome assessment: unclear, no details given. Documentation of exclusion: 28 women (19%) in the control group were excluded, no details given for the exclusion. Use of placebo control: no placebo control.
Participants	150 women were recruited into the study. Women with a luteal phase defect, as described by a peak serum P level < 120 mg/mL in the mid-luteal phase measured at 3 time points, were eligible and invited to participate. Luteal phase defects were ascertained in 2 consecutive menstrual cycles, and the third cycle was the intervention cycle. Women receiving IVF-ET treatment were excluded. 313 women were considered for enrolment in the study, 150 (48%) were randomised. 28 women were withdrawn from the control group, leaving 122 women in the study, who were allocated to vitamin C (n = 76) or control (n = 46). 5 women in the control group and 19 women in the vitamin C group became pregnant during the study period.
Interventions	Women in the intervention group took 750 mg vitamin C per day from the first day of the third menstrual cycle until a urinary pregnancy test was positive. Pregnancy rate was checked up until 6 months af-

Hemmi 2003 *(Continued)*

	ter the study cycle was started. Women in the control group received no supplementation and no treatment was given in the third cycle.
Outcomes	1. Serum P concentrations. 2. Serum E2 (oestrogen) concentrations. 3. Pregnancy rate. 4. Miscarriage.
Notes	Women's risk of spontaneous or recurrent miscarriage was unclear according to criteria specified in the review. Their dietary intake of vitamin C is unknown. No sample-size calculation was reported. Analyses were not based on intention to treat. Compliance: no details of any compliance assessments were given. Country: Japan. Time frame: January 1997 to December 2000. The denominators used for this trials are the number of women randomised and with a confirmed pregnancy (i.e. 19 for the vitamin group and 5 for the control group).

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Methodological details unclear.
Allocation concealment (selection bias)	Unclear risk	Methodological details unclear.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Methodological details unclear.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No methodological details are given.
Incomplete outcome data (attrition bias) All outcomes	High risk	28 women (19%) in the control group excluded.
Selective reporting (reporting bias)	Unclear risk	No details of exclusion of women in the control group given.
Other bias	High risk	No placebo control.

ICMR 2000

Methods	Randomisation and allocation concealment: unclear, "containers of vitamin or placebo capsules were given a random number" and "the key to random numbers was kept at the ICMR Headquarters". No other methodological details were given. Blinding of outcome assessment: "double blind" mentioned in the text, but no details given. Documentation of exclusion: 187 women (40%) were excluded from the analysis.

ICMR 2000 *(Continued)*

	Use of placebo control: placebo control.
Participants	466 women were recruited into the study. Women who had previously given birth to a child with an open NTD, and planned to have another child were eligible and invited to participate. This was regardless of their parity, number of previous births with an NTD, age, consanguinity, and socioeconomic status. Women who had previously given birth to a child with closed spina bifida, or with a history of diabetes or abnormal fasting and post-prandial blood sugar, history of epilepsy, congenital anomalies indicative of a genetic syndrome in the previous NTD, history of vitamin intake in the 3 months prior to enrolment, and pregnancy were excluded. 466 women were enrolled and randomised to either vitamin (n = 231) or placebo (n = 235), of these women, 90 were lost to follow-up immediately and 71 did not conceive until the final follow-up. Of the remaining 305 women who were known to become pregnant (vitamin n = 152, placebo n = 153), pregnancy outcomes were unknown for 26 women. In the paper, 279 of the initial 466 women were included in the analysis; however, in this review results are presented for main outcomes on an intention-to-treat basis (i.e. n = 466).
Interventions	The folic acid containing multivitamin included 120 mg ferrous sulphate, 240 mg calcium phosphate, 4000 IU vitamin A, 400 IU vitamin D, 2.5 mg vitamin B1, 2.5 mg vitamin B2, 2 mg vitamin B6, 15 mg nicotinamide, 40 mg vitamin C, 4 mg folic acid, 10 mg zinc. The placebo tablets contained the following trace elements: 120 mg ferrous sulphate and 240 mg calcium phosphate. Both capsules were identical in appearance and women were provided with the tablets from at least 28 days before conception and continuing until at least the second missed menstrual period.
Outcomes	1. Recurrence of NTDs. 2. Live births. 3. Stillbirths. 4. Spontaneous and induced abortion. 5. Multiple birth.
Notes	The risk profile of women in the trial for spontaneous and recurrent miscarriage is unclear, as is the dietary intake of participants. Sample-size calculation performed, assuming a 20% drop out rate. The trial was terminated after publication of the MRC trial in 1991. Compliance: compliance was assessed at 3-monthly visits, by checking a diary card maintained by the woman and the number of capsules returned. If the total number of missed days in 3 months did not exceed 10 days, and the total number of missed days at a stretch did not exceed 3, compliance was taken as satisfactory. Women not meeting the above criteria were excluded if they became pregnant in that particular quarter. No compliance data are specifically reported. Analyses not based on intention-to-treat. Country: India. Time frame: 1988 to 1991. The denominators used for this trial are based on the number of women randomised (i.e. 231 for the vitamin group and 235 for the placebo group). There was not enough information to accurately confirm the number of women that did or did not become pregnant due to the large number of losses to follow-up.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Containers 'given a random number'.
Allocation concealment (selection bias)	Unclear risk	'Key to random numbers were kept at the ICMR headquarters' but no other details given.
Blinding of participants and personnel (performance bias)	Unclear risk	Double-blind mentioned in the text but no details given.

ICMR 2000 *(Continued)*

All outcomes		
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Unclear of outcome assessors were unaware of treatment allocation.
Incomplete outcome data (attrition bias) All outcomes	High risk	187 (40%) women excluded.
Selective reporting (reporting bias)	Unclear risk	Difficult to assess given the high losses to follow-up.
Other bias	Unclear risk	Limited methodological details provided.

Jauniaux 2004

Methods	Randomisation and allocation concealment: randomised controlled trial, but no other information provided. Blinding of outcome assessment: unclear. Documentation of exclusions: unclear, no information provided. Use of placebo: placebo control.
Participants	Women with a history of 2 or more early pregnancy losses, with no identifiable cause for the losses.
Interventions	Vitamin C 1000 mg and vitamin E 400 IU versus placebo.
Outcomes	Miscarriage.
Notes	Updated 27/11/2013: the trial was stopped in October 2009 due to poor recruitment and lack of funding. Women's risk of spontaneous and recurrent miscarriage is unclear. Sample-size calculation: not done. No intention-to-treat analyses: not done. Compliance: unclear. Location: UK. Timeframe: recruitment planned from 2000 to 2001, but trial stopped in 2009.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Could not be assessed because the trial was stopped.
Allocation concealment (selection bias)	Unclear risk	Could not be assessed because the trial was stopped.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Could not be assessed because the trial was stopped.

Jauniaux 2004 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Could not be assessed because the trial was stopped.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Could not be assessed because the trial was stopped.
Selective reporting (reporting bias)	Unclear risk	Could not be assessed because the trial was stopped.
Other bias	Unclear risk	Could not be assessed because the trial was stopped.

Katz 2000

Methods	Randomisation and allocation concealment: cluster-randomised. 270 centres in the Salarhi district, Nepal, were involved which included 30 subdistricts each with 9 wards. Each ward was assigned to 1 of 3 treatment groups. "Wards were assigned by a random draw of numbered chits, blocked on subdistrict." Blinding of outcome assessment: women and study investigators were not aware of the treatment codes. Maternal mortality was assessed by study investigators blinded to treatment allocation, no details were given for other outcomes. Documentation of exclusions: 157 (1%) women were lost to follow-up and excluded. Use of placebo: placebo control.
Participants	15,832 women were recruited into the study. All married women of child bearing age in the Salarhi district, Nepal, were eligible and invited to participate in the study. Women migrating into the study area, or women that were never pregnant or refused participation, or women who migrated before being pregnant, were excluded from the analysis. Eligible women were identified from census data and marriage registers. 44,646 women were recruited, of which 1136 (2.5%) were excluded as they either emigrated before becoming pregnant, died or refused consent. During the study period 15,832 women identified themselves as being pregnant, and 157 women were lost to follow-up in the postpartum period. Results are reported for 17,373 pregnancies, allocated to the following groups: vitamin A (n = 6070), beta-carotene (n = 5650) or placebo (n = 5653). Denominators for the treatment groups vary for the measures of early infant mortality, due to losses to follow-up after birth.
Interventions	The 3 treatment groups consisted of a weekly single oral supplement of either: 1. 23,300 IU preformed vitamin A as retinyl palmitate; 2. 42 mg of all trans beta-carotene; 3. placebo. All capsules contained mg dl-alpha-tocopherol as an antioxidant. Women took the tablets prior to conception, during pregnancy and postpartum, for a total of 3.5 years.
Outcomes	1. Fetal loss, defined as any reported miscarriage, stillbirth or maternal death during pregnancy. The outcomes were based on self-reports, and women who reported to be pregnant for >= 6 weeks but then no longer reported being pregnant were considered to have had a miscarriage. Serial publications also reported neonatal death.
Notes	Women's risk profile for spontaneous or recurrent miscarriage was unclear, as was their dietary intake of vitamin A. Compliance: women were distributed the capsules in their home on a weekly basis, receipt of capsules was noted only if the distributor observed the woman swallowing the capsule. Over half of the women

Katz 2000 *(Continued)*

who became pregnant during the study received over 80% of their intended supplements, and 75% of pregnant women received at least half of their eligible doses.
There were serial publications of this study causing the study numerators and denominators to vary between published versions, and multiple pregnancy figures reported did not include higher order pregnancies.
Sample-size calculation performed.
Partial intention-to-treat analyses, and the risk ratios and confidence intervals were adjusted to account for any cluster-design effect.
Country: Nepal.
Timeframe: April 1994 to September 1997.
The denominators used for this trial are the number of women randomised who identified themselves as pregnant (i.e. 6070 for the vitamin A group, 5650 for the beta-carotene group and 5653 for the placebo group).

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Cluster-randomised, unclear how sequence was generated.
Allocation concealment (selection bias)	Unclear risk	Each ward was assigned to the treatment groups based on 'a random draw of numbered chits, blocked on subdistrict'.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Women and investigators blinded to treatment allocation.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	"This committee and the data analysts were unmasked to the treatment codes, but the codes were made available to study investigators only at the end of the trial."
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	157 women (1%) were lost to follow-up and excluded, partial intention-to-treat analysis performed.
Selective reporting (reporting bias)	Unclear risk	Denominators vary in several publications of this trial.
Other bias	High risk	Some women were pregnant more than once during the study period, however the denominators reported are the total number of pregnancies during the study period, not the total number of women randomised, which incorrectly assumes that each data point included is independent from the next.

Kirke 1992

Methods	Randomisation and allocation concealment: block randomisation, stratified by hospital, using "consecutively numbered, opaque, sealed envelopes". Blinding of outcome assessment: women and study investigators were initially blinded to the treatment allocation, however the tablet preparations were changed after 55 women were randomised and after this only participants were blinded. Documentation of exclusion: 3 women (1%) were lost to follow-up and excluded. Use of placebo control: 3 treatment regimens were assessed, no placebo control.

Kirke 1992 *(Continued)*

Participants	354 women were recruited into the study. Women with a previous NTD defined as anencephalus, inien-cephalus, encephalocoele, and spina bifida aperta, who were not pregnant when contacted but were planning a future pregnancy, were eligible and invited to participate. Women were identified from case registers at the participating hospitals. Women with conditions likely to result in impaired absorption from the gastrointestinal tract were excluded. 435 women were approached, of which 354 (84%) consented and were randomised to either F (n = 115), MV (n = 119) or MF (n = 120). 16 women did not become pregnant, and 75 women withdrew; however, their pregnancy outcome status was known, and 18 of these women subsequently became pregnant after withdrawing. 3 women were lost to follow-up. 281 women (93 in the F group, 93 in the MF group and 95 in the MV group) became pregnant in the study period and their pregnancy outcome was known.
Interventions	Indistinguishable trial tablets were initially made by Beecham and Glaxo, however Beecham withdrew their support after 55 women had been randomised. After this time a commercially available pregnavite Forte F was used (MF tablet) and Antigen Pharmaceuticals produced a white multivitamin tablet without folic acid. This was associated with a loss of blinding. Women were randomised to 1 of 3 treatments: 1. folic acid alone (F); 2. multivitamin with folic acid (MF); 3. multivitamin with no folic acid (MV). The F and MF resulted in a daily dose of 0.3 mg folic acid. The MF and MV resulted in a daily dose of 4000 IU vitamin A, 400 IU calciferol, 1.5 mg thiamine hydrochloride, 1.5 mg riboflavine, 1 mg pyridoxine hydrochloride, 15 mg nicotinamide, 40 mg ascorbic acid, 480 mg calcium phosphate, and 252 mg ferrous sulphate. Women took the tablets for at least 2 months prior to conception and until the date of the 3rd missed period.
Outcomes	1. Recurrence risk of NTDs. 2. Spontaneous abortion. 3. Ectopic pregnancy. 4. Livebirth. 5. Stillbirth. 6. Congenital malformations excluding NTDs.
Notes	The trial was stopped after there were poor recruitment rates and birth rates. A sample-size calculation required 462 women to show a reduction in NTDs from 5% to 1%. Data from 106 women who were already pregnant at time of recruitment are also included. The risk profile of women in the trial for spontaneous and recurrent miscarriage is unclear, as is their dietary intake. Compliance: compliance was assessed on tablet counts and blood tests; however, the results are not presented. Intention-to-treat analyses were performed. Location: Republic of Ireland. Timeframe: December 1981 to January 1988. The denominators used for this trial are the number of women randomised who became pregnant in the study period and their pregnancy outcome was known (i.e. 93 in the F group, 93 in the MF group and 95 in the MV group).

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Block randomisation stratified by hospital site.
Allocation concealment (selection bias)	Low risk	Consequtively numbered, opaque sealed envelopes used.

Kirke 1992 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Low risk	Only participants were blinded.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Only participants were blinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	3 women (1%) lost to follow-up and excluded. Intention-to-treat analyses performed.
Selective reporting (reporting bias)	Unclear risk	Compliance data not reported.
Other bias	High risk	The trial was stopped after there were poor recruitment rates and birth rates.

Kumwenda 2002

Methods	Randomised controlled trial of vitamin A, iron and folic acid supplementation versus iron and folic acid only, during pregnancy, to improve infant outcomes born to women infected with HIV in Malawi. Randomisation and allocation concealment: "treatment assignment was determined by use of a computer's random-number generator" and "mothers were assigned an original study identification number at enrolment and were given the next sequentially numbered opaque bottle with supplements". "Treatment assignment was concealed by pre packing study supplements in sequentially numbered series assigned to study identification numbers." Blinding of outcome assessment: unclear, not specifically stated, but participants were blind to their treatment allocation. Documentation of exclusion: 63 (9%) women were lost to follow-up and 14 (2%) pairs of twins were excluded. Use of placebo control: control tablets containing iron and folic acid were given.
Participants	Pregnant women between 18 and 29 weeks' gestation and infected with HIV. The average gestation of participants was 23 weeks. 693 women were enrolled and allocated to either vitamin A (n = 340) or control (n = 357), of which pregnancy outcomes were known for 623 women. 63 women were lost to follow-up and 14 sets of twins were excluded due to their higher risk of low birthweight and infant mortality.
Interventions	All women received orally administered daily doses of 30 mg iron and 400 mcg folic acid during the study. Women in the intervention group received 10,000 IU vitamin A (3 mg retinol equivalent) orally, in addition to the iron and folic acid supplements. Women were asked to take the tablets from enrolments until delivery. Tablet counts were conducted every 4 weeks. All women received 30 mg retinol equivalents at 6 weeks postpartum, according to standard postpartum care in Malawi.
Outcomes	1. Infant Hb level at 6 weeks and 12 months of age. 2. Percentage of infants with anaemia at 6 weeks of age and at 12 months, defined as a Hb level of < 110 g/L. 3. Birthweight. 4. Percentage of infants < 2500 g at birth. 5. Weight and length at 6 weeks, 14 weeks and 6 months of age. 6. Transmission of HIV to the infant, infant mortality at < 6 weeks of age, at 12 months and at 24 months.

Kumwenda 2002 *(Continued)*

	7. Stillbirth and spontaneous abortion (undefined).
Notes	Women's risk of spontaneous and recurrent miscarriage is unclear, although may be increased due to their HIV status. 50% of women in the vitamin A group and 51% of women in the control group had deficient levels of vitamin A (defined as plasma vitamin A < 0.70 umol/L) at trial entry. Sample-size calculation performed. No intention-to-treat analyses were performed. Compliance: more than 95% of women in both groups took > 90% of study supplements, as ascertained by tablet counts. Location: Malawi. Timeframe: November 1995 to December 1996.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated random number list.
Allocation concealment (selection bias)	Low risk	Sequentially number opaque bottles used.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not specifically stated but women were blinded.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Unclear of outcome assessors were unaware of treatment allocation.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	63 women (9%) lost to follow-up and 14 pairs of twins (2%) excluded. No intention-to-treat analyses performed.
Selective reporting (reporting bias)	Low risk	All pre-specified outcomes appear to be reported.
Other bias	Unclear risk	Insufficient information to assess whether an important risk of other bias exists.

McCance 2010

Methods	Randomisation and allocation concealment: participants were randomly allocated in a 1:1 ratio to receive 1000 mg vitamin C and 400 IU vitamin E. A randomisation sequence generated in advance by Victoria Pharmaceuticals using PRISYM ID software (version1.0009) was used. The randomisation sequence was stratified by centre with balanced blocks of 8 patients and was held by Victoria Pharmaceuticals. Individual sealed envelopes containing treatment allocations were given to trial pharmacists in every centre allowing treatment groups to be revealed in a clinical emergency. Blinding of outcome assessment: diagnosis was independently confirmed by 3 senior clinicians, who were unaware of treatment allocation. Documentation of exclusion: only 1 loss to follow-up was reported. Use of placebo control: matched placebo control.

McCance 2010 *(Continued)*

Participants	762 pregnant women between 8 and 22 weeks' gestation with type-1 diabetes attending 25 antenatal metabolic clinics across Northern Ireland, Scotland, and northwest England. Participants were women with type 1 diabetes preceding pregnancy, presentation between 8 weeks' and 22 weeks' gestation, singleton pregnancy, and age 16 years or older. Women with chronic hypertension were included in the trial. Women were excluded if they did not give consent, were enrolled in another research study, were being treated with warfarin, or were known to misuse drugs Women taking vitamin supplements were excluded only if these contained 500 mg or more vitamin C or 200 IU or more vitamin E daily.
Interventions	1000 mg vitamin C and 400 IU vitamin E versus matched placebo started between 8 and 22 weeks' gestation and taken until delivery.
Outcomes	1. Pre-eclampsia. 2. Placental and endothelial function (established by PAI-1 to PAI-2 ratio). 3. Gestational hypertension. 4. Birthweight (centile as calculated from customised birthweight charts). 5. Miscarriage. 6. Maternal death. 7. Obstetric complications and other adverse outcomes. 8. Fetal malformation. 9. Gestational age at delivery. 10.Admission to a neonatal care unit.
Notes	Women's risk profile for spontaneous and recurrent miscarriage: women with chronic hypertension were included. Multivitamin supplementation at randomisation was reported at trial entry. Other information about nutrition status are not provided. Sample-size calculation: based on 40% reduction in pre-eclampsia. Modified intention to treat was used for analysis of the primary endpoint. Compliance: unused tablets and capsules were collected during delivery admission or at the 6-week postnatal trial visit, or were returned in postage prepaid envelopes. Location: Northern Ireland, Scotland, northwest England. Tiimeframe: April 2003 to June 2008.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated randomisations by Victoria Pharmaceuticals using PRISYM ID software (version1.0009).
Allocation concealment (selection bias)	Low risk	Supplements were identical in appearance. The randomisation sequence was stratified by centre with balanced blocks of 8 patients, and was held by Victoria Pharmaceuticals.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Treatment allocation was masked from all trial personnel and participants until trial completion.
Blinding of outcome assessment (detection bias)	Low risk	Diagnosis were independently confirmed by 3 senior clinicians, who were unaware of treatment allocation.

McCance 2010 *(Continued)*

All outcomes		
Incomplete outcome data (attrition bias) All outcomes	Low risk	Only 1 loss to follow-up in placebo group, but the reason is unclear.
Selective reporting (reporting bias)	High risk	Fewer outcomes were stated in the trial registration.
Other bias	Low risk	The study appears to be free of other sources of bias.

MRC 1991

Methods	Randomisation and allocation concealment: third party randomisation, "randomisation was carried out through the Clinical Trials Service Unit in Oxford". Randomisation was stratified by centre. Blinding of outcome assessment: women, caregivers and study investigators were blinded to the treatment allocation. Documentation of exclusion: 164 women (9%) excluded. Use of placebo control: placebo control.
Participants	1817 women were recruited into the study. Women who had a previous pregnancy affected by a NTD, and were planning another pregnancy and not already taking supplements were eligible for the study. Women whose affected child had Meckel's syndrome and those women with epilepsy were excluded. 1817 women were randomised to either F (n = 449), MV (n = 453), MF (n = 461) or P (n = 454), of which, 1195 were informative pregnancies that is, where the outcome of NTD or not was definitely known (F n = 298, MV n = 302, MF n = 295, P n = 300). Results for pregnancy loss are reported for both informative and not informative pregnancies. 164 women were excluded as they may have been pregnant at the time of randomisation.
Interventions	Women were randomised into 1 of 4 groups: 1. 4 mg, 240 mg di-calcium phosphate and 120 mg ferrous sulphate (F); 2. 4000 IU vitamin A, 400 IU calciferol, 1.5 mg thiamine hydrochloride, 1.5 mg riboflavine, 1 mg pyridoxine hydrochloride, 15 mg nicotinamide, 40 mg ascorbic acid, 240 mg di-calcium phosphate and 120 mg ferrous sulphate (MV); 3. folic acid combined with the multivitamins specified above (MF); 4. placebo containing 240 mg di-calcium phosphate and 120 mg ferrous sulphate only (P). Women took the tablets prior to conception and attended the site every 3 months to collect additional supplies and again during the 12th week of pregnancy. No special dietary advice was given to women.
Outcomes	1. NTD and other birth defects. 2. Spontaneous abortions. 3. Ectopic pregnancy. 4. Termination or pregnancy. 5. Livebirth. 6. Stillbirth. 7. Multiple pregnancy. 8. Subsequent publications report on blood folic acid and zinc concentrations.
Notes	The trial was stopped early after there were 1195 informative pregnancies, according to prespecified stopping rules. The aim of the study was to obtain information on at least 2000 informative pregnancies unless a sufficiently clear result emerged sooner.

MRC 1991 *(Continued)*

	Women's risk profile for spontaneous and recurrent miscarriage was unclear, as was their nutritional status. Compliance: compliance based on self-reports, and data were available for women with an informative pregnancy only, where 79 (6%) women reported they stopped taking their capsules before their last scheduled visit. Intention-to-treat analyses are reported in this review including not informative pregnancies (i.e. n = 1817). Location: multi-national study co-ordinated from the UK. Timeframe: July 1983 to April 1991. The denominators used for this trial are the number of women randomised, i.e. (449 for the F group, 453 for the MV group, 461 for the MF and 454 for the P group). There was no information provided about any women randomised that did not become pregnant in the study period.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Third party randomisation, "randomisation was carried out through the Clinical Trials Service Unit in Oxford".
Allocation concealment (selection bias)	Low risk	Third party randomisation, "randomisation was carried out through the Clinical Trials Service Unit in Oxford".
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Women, caregivers and investigators blinded to treatment allocation.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No details are given if outcome assessment was blinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	164 women (9%) excluded, intention-to-treat analyses performed.
Selective reporting (reporting bias)	Unclear risk	No information provided about any women randomised that did not become pregnant in the study period.
Other bias	High risk	The trial was stopped early after there were 1195 informative pregnancies, according to prespecified stopping rules.

Osrin 2005

Methods	Randomisation and allocation concealment: 1 of the authors 'randomly allocated 1200 participant numbers by computer into 2 groups in permuted blocks of 50'. Every identification number was allocated a supplement container, which was then packed by a team member not otherwise involved in the trial. After enrolment, another author allocated participants sequential identification numbers with the corresponding supplement containers. Blinding of outcome assessment: double-blind stated but no other details given. Documentation of exclusion: 61 women (5%) withdrew or were lost to follow-up, however data on miscarriage were reported for those who withdrew due to miscarriage. Use of placebo control: control of iron and folic acid supplements given which looked identical to the intervention supplements.

Osrin 2005 *(Continued)*

Participants	1200 women were recruited into the study. Women were eligible if they were: less than 20 completed weeks, had a singleton pregnancy, no notable fetal abnormality, no existing maternal illness of a severity that could compromise the outcome of pregnancy, and lived in an area of Dhanusha or the adjoining district of Mahottari accessible for home visits. Maternal illnesses that led to exclusion were: recently treated recurrent cysticercosis, need for chlorpromazine or anticoagulant drugs with changing doses, and symptomatic mitral stenosis or multivalvular heart disease. Fetal exclusions were: twin pregnancies, anencephaly, occipital meningocele, encephalocele, duodenal atresia and a grossly dilated pelvicalyceal system.
Interventions	Intervention group: vitamin A 800 mcg, vitamin E 10 mg, vitamin D 5 mcg, vitamin B1 1.4 mg, vitamin B2 1.4 mg, niacin 18 mg, vitamin B6 1.9 mg, vitamin B12 2.6 mcg, folic acid 400 mcg, vitamin C 70 mg, iron 30 mg, zinc 15 mg, copper 2 mg, selenium 65 mcg, and iodine 150 mcg. Control group: iron 60 mg and folic acid 400 mcg. Supplementation began at a minimum of 12 weeks' gestation and continued until delivery.
Outcomes	1. Birthweight. 2. Gestational duration. 3. Infant length and head circumference. 4. Miscarriage defined as cessation of confirmed pregnancy before 23 weeks' gestation. 5. Stillbirth defined as delivery of an infant showing no signs of life (movement, breathing, or heartbeat) after 23 weeks' gestation. 6. Early neonatal death defined as death of a live born infant in the first 7 days after birth. 7. Late neonatal death as death of a live born infant after 7 but within 28 days.
Notes	Women's risk of spontaneous and recurrent miscarriage was unclear. Women's nutritional status is also unclear, however, women are presumable at high risk of under-nutrition as the paper states that in Nepal 'deficiencies of several micronutrients have been well described in individual studies and in a national sample'. Intention-to-treat analyses performed. Compliance: median 'adherence' was 98% in the control group and 97% in the intervention group. Location: Nepal. Timeframe: August 2002 to October 2003.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated in permuted blocks of 50.
Allocation concealment (selection bias)	Unclear risk	1 of the authors allocated participants with sequential identification numbers, but unclear if this person was involved in the recruitment of participants.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Double-blind stated in the text but no other details given.
Blinding of outcome assessment (detection bias) All outcomes	High risk	The allocation code was broken for the analysis. Pg 956.

Osrin 2005 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Low risk	61 women (5%) withdrew or were lost to follow-up, however data on miscarriage were reported for those who withdrew due to miscarriage. Intention-to-treat analyses performed.
Selective reporting (reporting bias)	Low risk	All pre-specified outcomes appear to be reported.
Other bias	Low risk	The study appears to be free of other sources of bias.

People's League 1942

Methods	Randomisation and allocation concealment: "women enrolled at the antenatal clinic were divided into two main groups by placing them alternatively on separate lists". Blinding of outcome assessment: unclear, no information given on blinding of participants, carers or outcome assessors. Documentation of exclusion: 622 women (11%) were excluded. Use of placebo control: no placebo given.
Participants	5644 women were recruited into the study. All women attending the antenatal clinics and who were less than or equal to 24 weeks' gestation and who were in 'good health' were eligible for the study. Women who were more than 24 weeks' gestation and women who suffered from any disease or physical abnormality were excluded from the study. After enrolment, women who had twin births and who miscarried at an early stage were also excluded. 5644 women were initially enrolled in the study of which 5022 (89%) remained in the study. Of the 622 (11%) women withdrawn from the trial, 494 were evacuated from the London area (due to World War 2), 39 women had twin births and 89 women miscarried at an early stage. 5022 women remained in the study and were allocated to either multivitamins (n = 2510) or control (n = 2512). Women were further divided into primiparae and multiparae, and various age groups.
Interventions	Women allocated to the treatment group were given daily vitamin C 100 mg, ferrous iron 0.26 g, calcium 0.26 g, minute quantities of iodine, manganese and copper, adsorbate of vitamin B1 containing all factors of the B complex and halibut liver oil 0.36 g containing vitamin A (52,000 IU per g) and vitamin D (2500 IU per g). Women allocated to the control group received no placebo.
Outcomes	1. Toxaemia classified into subgroups based on: hypertension only, albuminuria with or without hypertension, or hypertension with albuminuria (pre-eclampsia). 2. Maternal sepsis. 3. Length of gestation (categorised as less than 40 weeks, 40 weeks, and greater than 40 weeks). 4. Percentage of women breastfeeding. 5. Stillbirth. 6. Neonatal mortality (defined as death before 8 days). 7. Birthweight (pounds) (only reported for primiparae and multiparae separately).
Notes	Women risk status for spontaneous and recurrent miscarriage is unclear. Dietary intake at trial entry: "vitamin C shortage affected about half the women". Intention-to-treat analyses: not performed. Compliance: unclear, no information provided. Sample-size calculation: unclear. "It was decided that the investigation should include a minimum of 5000 pregnant women". No other details given. Location: England. Timeframe: 1938 to 1939.

People's League 1942 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Quasi-randomistion using alternate separate lists.
Allocation concealment (selection bias)	High risk	No allocation concealment.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No information about blinding provided.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No information about blinding provided.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	622 women (11%) excluded, intention-to-treat analyses not performed.
Selective reporting (reporting bias)	Unclear risk	Limited methodological details provided.
Other bias	Unclear risk	Limited methodological details provided.

Poston 2006

Methods	Randomisation and allocation concealment: the randomisation (computer-generated sequence) was blocked—i.e., balanced—by centre in groups of 2 to 10 individuals. Blinding of outcome assessment: none of the trial staff or any other person involved in the trial knew the allocated treatment of any woman until after completion of the study. Documentation of exclusion: 9 (0.4%) women were excluded. Use of placebo control: placebo control.
Participants	2404 women with clinical risk factors for pre-eclampsia Inclusion criteria: gestational age 14^{+0}–21^{+6} weeks; one or more of the following risk factors: pre-eclampsia in the pregnancy preceding the index pregnancy, requiring delivery before 37 completed weeks' gestation, diagnosis of HELLP syndrome in any previous pregnancy, eclampsia in any previous pregnancy; essential hypertension requiring medication, type 1 or type 2 diabetes, multiple pregnancy; abnormal uterine artery doppler waveform primiparity with BMI at first antenatal appointment of 30 kg/m^2 or more. Exclusion criteria: women unable or unwilling to give written informed consent or women who were being treated with warfarin. Women taking vitamin supplements that contained doses of vitamin C of 200 mg or more or of vitamin E of 40 IU or more daily were excluded.

Poston 2006 *(Continued)*

Interventions	Women were assigned to 1000 mg vitamin C and 400 IU vitamin E (RRR α tocopherol; n = 1199) or matched placebo (n = 1205) daily from the second trimester of pregnancy until delivery.
Outcomes	Primary outcomes 1. Pre-eclampsia, Secondary outcomes: 1. Low birthweight (<2·5 kg). 2. Small size for gestational age. 3. Preterm birth (≤37+^{0} weeks' gestation). 4. Gestational age at delivery. 5. Smaller than 10th centile for gestation. 6. Use of health-care resources.
Notes	Women risk status for spontaneous and recurrent miscarriage: history of chronic hypertension, BMI, pre-eclampsia, multiple pregnancy, diabetes, and other risk factors reported. Dietary intake at trial entry: use of supplements reported. Intention-to-treat analyses: not performed. Compliance: 80% (n = 1653) of women took at least 50% of their tablets, 65% (n = 1345) took 80% or more, and 32% (n = 661) took all of their tablets; 6% (n = 125) did not take any tablets. Sample-size calculation: expected incidence of pre-eclampsia in the placebo group of at least 15% and in the treatment group of at least 30% Location: 25 hospitals, UK. Timeframe: August 2003 to June 2005.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated random sequence Pg 1146
Allocation concealment (selection bias)	Unclear risk	Although paper states that supplementation and placebo looked and tasted the same, (Pg 1146) there is no clear description of how women were allocated to treatment group
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"none of the trial staff or any other person involved in the trial knew the allocated treatment of any woman until after completion of the study" Pg 1146
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Unclear from text if outcome assessors were blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	Very low loss to follow-up rates. In the supplementation group 3 (0.25%) losses to follow-up and in the placebo group 6 (0.5%).
Selective reporting (reporting bias)	Unclear risk	A large number of outcomes reported in the publication, but not pre-specified in the registered trial.
Other bias	Low risk	The study appears to be free of other sources of bias.

Prawirohartono 2011

Methods	Randomisation and allocation concealment: community-based, individually-randomised, placebo-controlled and double-blinded study. Pregnat women were randomly allocated in a 1:1:1:1 ratio in blocks of 12 based on a list of treatment numbers derived from a pseudo-random number generated with SAS software. Blinding of outcome assessment: all investigators, field and laboratory staff and participants were blinded to the treatment code until all field data had been collected and preliminary data analysis by coded groups had been completed. Documentation of exclusions: 75 women (3.5%) were excluded. Use of placebo control: placebo control.
Participants	2173 women at a gestational age of ,17 weeks were included in the study. Women at a gestational age of >=17 weeks were not eligible.
Interventions	Women were allocated to one of the three intervention groups: 1. 2400 retinol equivalents of vitamin A as retinyl palmitate, 2. 20 mg of zinc sulfate, or 3. the same dose of vitamin A and zinc sulfate. Comparison group: placebo. All capsules also contained 2mg dl-alpha-tocopherol as antioxidant and 350 mg of soyabean oil, 20 mg of beeswax and 8 mg of lecithin as capsule filler.
Outcomes	1. Birthweigh. 2. Birth length. 3. Neonatal morbidity. 4. Infant mortality.
Notes	Women's risk of spontaneous and recurrent miscarriage was unclear. Women's nutritional status is unclear Intention-to-treat analyses not performed. Sample-size calculation not performed Compliance: consumption of 70% of supplements. Location: Indonesia. Timeframe: September 1995 to December 1999.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Pregnant women were randomly allocated in a 1:1:1:1 ratio in blocks of 12 based on a list of treatment numbers derived from a computer-generated pseudo-random number
Allocation concealment (selection bias)	Unclear risk	Treatment allocations was prepared and held at the University of Newcastle ....Supplements were coded with treatment numbers and women were assigned a treatment number in sequence based on date they consented to par-

Prawirohartono 2011 *(Continued)*

		ticipate in the study. However, supplements were packed in plastic strips in identical opaque capsules..page 16 - 17.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	All investigators, field and laboratory staff and participants were blinded to the treatment code until all field data had been collected and preliminary data analysis by coded groups had been completed page 17
Blinding of outcome assessment (detection bias) All outcomes	Low risk	All investigators, field and laboratory staff and participants were blinded to the treatment code until all field data had been collected and preliminary data analysis by coded groups had been completed page 17
Incomplete outcome data (attrition bias) All outcomes	Low risk	Drop-out rate appears balanced between groups and reasons for loss to follow-up were provided.
Selective reporting (reporting bias)	Low risk	Study protocol unavailable but outcomes predefined outcomes were reported
Other bias	Unclear risk	Overall, 70% of supplements were consumed, but it is unclear in text where there was more or less compliance.

Roberfroid 2008

Methods	Randomisation and allocation concealment: the randomisation scheme was generated by a computer program in permuted blocks of 4. Randomisation numbers were sealed in opaque envelopes. At each inclusion, the consulting physician opened the next sealed envelope and transmitted the randomisation number to a pharmacist managing the allocation sequence and the packaging of drugs at a central location. Blinding of outcome assessment: the consulting physicians, pharmacist and women were blinded to allocation. Documentation of exclusions: 107 women were lost to follow-up (however their pregnancy outcome was reported). Post randomisation 26 twins were excluded (multivitamin group: 15; iron/folic acid group: 11 twins (including 1 set of triplets). Only singleton pregnancies were included in the analysis because fetal loss and anthropometric measures at birth in multiple pregnancies are not primarily nutrition-related. 3 women died before delivery and 1 woman underwent a therapeutic abortion. Use of placebo control: no placebo.
Participants	1374 women were recruited to participate, however 52 women were randomly assigned twice for consecutive pregnancies, resulting in data for 1426 pregnancies. Women had a pregnancy confirmed by urine testing and were randomly assigned to receive either IFA (n = 712) or UNIMMAP (n = 714) daily until 3 months after delivery. Women were recruited between 5 to 36 weeks' gestation; 34.6% (n = 493) of the participants were recruited in the first trimester of pregnancy, mean gestational age at enrolment was 17.3 weeks (SD 7.8 weeks).
Interventions	UNIMMAP: vitamin A 800 mcg, vitamin D 200 IU, vitamin E 10 mg, vitamin B-1 1.4 mg, vitamin B-2 1.4 mg, niacin 18 mg, folic acid 400 mcg, vitamin B-6 1.9 mg, vitamin B-12 2.6 mcg, vitamin C 70 mg, zinc 15 mg, iron 30 mg, copper 2 mg, selenium 65 mcg, iodine 150 mcg. IFA (control): folic acid 400 mcg, Iron 60 mg. In a case of maternal illness, appropriate treatments were provided according to national guidelines. Severely anaemic women (Hb < 70 g/L, without dyspnoea) received ferrous sulphate (200 mg) + folic acid (0.25 mg) twice daily, for 3 months, regardless of their allocation group. All participants also received 400 mg albendazole in the second and third trimesters. If malaria occurred despite chemopro-

Roberfroid 2008 *(Continued)*

	phylaxis, quinine (300 mg, 3 times/day) was given for 5 days. Vitamin A (200,000 IU) was given to all women after delivery, in accordance with national recommendations.
Outcomes	1. Gestational duration. 2. Birthweight, birth length, and Rohrer ponderal index at birth (weight(g)X100/length3(cm)). 3. Low birthweight (< 2500 g). 4. Small-for-gestational age (birthweight below the 10th percentile). 5. Large-for-gestational age (birthweight above the 90th percentile of the study population). 6. Thoracic circumference, head circumference, mid upper arm circumference. 7. Hb concentration in mothers during the third trimester, Hb and sTfR concentrations in cord blood. 8. Preterm birth (< 37 weeks' gestation). 9. Stillbirth (delivery of an infant showing no sign of life after a gestational age of 28 weeks). 10. Perinatal death.
Notes	Women's risk of spontaneous and recurrent miscarriage was unclear. 18% of women in each group had experienced a previous fetal loss. Women's nutritional status is unclear, although women are presumable at risk as the purpose of the trial is to correct MMN deficiencies. Intention-to-treat analyses not performed, however the review included details of losses to follow-up where the outcome was known. Compliance: unclear, states that there was no difference in compliance between the 2 groups. Location: Burkino Faso. Timeframe: March 2004 to October 2006.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated with permuted blocks of 4.
Allocation concealment (selection bias)	Low risk	Randomisation numbers were kept in sealed opaque envelopes.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Consulting physicians, pharmacist and women were blinded to the intervention.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Authors claim the study had double-blind design, but it is unclear if the assessors were blinded.
Incomplete outcome data (attrition bias) All outcomes	High risk	Data were reported for singletons only.
Selective reporting (reporting bias)	Unclear risk	As above - data only reported for singletons.
Other bias	High risk	Some women were pregnant more than once during the study period, however the denominators reported are the total number of pregnancies during the

Roberfroid 2008 *(Continued)*

	study period, not the total number of women randomised, which incorrectly assumes that each data point included is independent from the next.

Roberts 2010

Methods	Randomisation and allocation concealment: women were randomly assigned to receive capsules containing a combination of 1000 mg of vitamin C (ascorbic acid) and 400 IU of vitamin E (RRR-alpha-tocopherol acetate) or matching placebo (mineral oil). The simple urn method, with stratification according to clinical centre, was used by the data co-ordinating centre to create a randomisation sequence. No further methodological details are provided. Blinding of outcome assessment: medical charts were reviewed by at least 3 reviewers who were unaware of the treatment assignments. Documentation of exclusions: 183 women (1.8%) were lost to follow-up and for 2 women had been removed after randomisation. Use of placebo control: placebo given.
Participants	10,154 pregnant women who had a singleton fetus with a gestational age of less than 16 weeks 0 days at the time of screening attending 16 clinical centres and the independent data coordinating centre of the MFMU Network. Women were eligible for inclusion if they had not had a previous pregnancy that lasted beyond 19 weeks 6 days. Women were not eligible if they had elevated systolic or diastolic blood pressure, proteinuria, were taking or had taken antihypertensive medication, or were taking more than 150 mg of vitamin C or more than 75 IU of vitamin E daily. Other exclusion criteria were diabetes that was present before the pregnancy, treatment with antiplatelet drugs or non-steroidal anti-inflammatory agents, uterine bleeding within the week before recruitment, uterine malformation, serious medical condition, known fetal anomaly or aneuploidy, in vitro fertilisation resulting in the current pregnancy, or abuse of illicit drugs or alcohol.
Interventions	A combination of 1000 mg of vitamin C (ascorbic acid) and 400 IU of vitamin E daily administered from enrolment until delivery. The control group received placebo.
Outcomes	1. Pregnancy-associated hypertension. 2. Serious adverse outcomes in the mother or her fetus or neonate. Pre-eclampsia. 3. Other maternal and neonatal outcomes.
Notes	Women's risk of spontaneous and recurrent miscarriage was unclear. Use of prenatal vitamins or multivitamins, daily dose of vitamin C and E were reported at trial entry. Sample size calculation was based on a 30% reduction in the rate of the primary outcome. Intention-to-treat analysis was performed. Compliance: monthly, participants returned unused study drugs from the previous month. Location: UK. Timeframe: July 2003 to February 2008.

Risk of bias

Bias	Authors' judgement	Support for judgement

Roberts 2010 *(Continued)*

Random sequence generation (selection bias)	Low risk	"The simple urn method, with stratification according to clinical center, was used by the data coordinating center to create a randomization sequence." pg 1283, last pgh.
Allocation concealment (selection bias)	Unclear risk	Text says participants "were randomly assigned to receive capsules containing...". No details on how participants were allocated to groups. pg 1283 last pgh.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"Neither the participants nor the investigators were aware of the treatment assignments." pg 1283, last pgh.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"Deidentified medical charts of all women with pregnancy-associated hypertension were reviewed centrally by at least three reviewers who were unaware of the treatment assignments." pg 1284.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Vitamin C and E = 95/5088 missing and in placebo = 90/5066 missing. Reasons for missing similar between groups.
Selective reporting (reporting bias)	Low risk	Relevant outcomes reported as pre-specified in the protocol.
Other bias	Low risk	The study appears to be free of other sources of bias.

Rumbold 2006

Methods	Randomisation and allocation concealment: computer-generated random number list with balanced variable blocks and stratification for collaborating centre and gestational age (< 18 weeks versus 18 weeks or more), allocation occurred via a central telephone randomisation service. The treatment packs contained 4 sealed, opaque, white plastic bottles of either the antioxidants vitamin C and vitamin E or the placebo and were prepared by a researcher not involved in recruitment or clinical care. Blinding of outcome assessment: women, caregivers and investigators were blinded to allocation. Documentation of exclusion: no losses to follow-up. Use of placebo control: placebo given.
Participants	1877 women were recruited into the study. Eligible women included those: with a nulliparous singleton pregnancy, between 14 and 22 weeks of gestation and with normal blood pressure at the first measurement in pregnancy and again at trial entry. Women who had any of the following were excluded: known multiple pregnancy, known potentially lethal fetal anomaly, known thrombophilia, chronic renal failure, antihypertensive therapy, or specific contraindications to vitamin C or E therapy such as haemochromatosis or anticoagulant therapy. Women were allocated to the vitamin C and E group (n = 935) or placebo (n = 935).
Interventions	Women allocated to the vitamin C and E group took 4 coated tablets of a combination of 250 mg of vitamin C (as ascorbic acid) and 100 IU of vitamin E (as *d*-alpha-tocopherol succinate) each day from trial entry until delivery (total daily dose of vitamin C: 1000 mg; vitamin E: 400 IU). Women were advised not to take any other antioxidant supplements, although a multivitamin preparation that provided a daily intake of no more than 200 mg of vitamin C or 50 IU of vitamin E was permitted.

Rumbold 2006 *(Continued)*

Outcomes	1. Pre-eclampsia. 2. A composite measure of death or serious outcomes in the infant. 3. Small-for-gestational age. 4. Serious infant complications occurring before hospital discharge. 5. For women included a composite of any of the following until 6 weeks postpartum: death, pulmonary edema, eclampsia, stroke, thrombocytopenia, renal insufficiency, respiratory distress syndrome, cardiac arrest, respiratory arrest, placental abruption, abnormal liver function, preterm prelabour rupture of membranes, major postpartum haemorrhage, postpartum pyrexia, pneumonia, deep-vein thrombosis, or pulmonary embolus requiring anticoagulant therapy.
Notes	Women were at low risk of spontaneous and recurrent miscarriage based on the review criteria. The majority of women participating had a baseline dietary intake of vitamin C and E above the Australian recommended daily amount. Intention-to-treat analyses performed. Compliance: there was no difference in compliance between the vitamin group (67%) and the placebo group (70%). Location: Australia. Timeframe: December 2001 and January 2005.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated random number list.
Allocation concealment (selection bias)	Low risk	Allocation occurred via a central telephone randomisation service. Tablets were provided in sealed opaque bottles.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Women, caregivers and investigators were blinded.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No information provided about blinding of outcome assessment.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No losses to follow-up.
Selective reporting (reporting bias)	Low risk	All pre-specified outcomes reported.
Other bias	Low risk	The study appears to be free of other sources of bias.

Rumiris 2006

Methods	Generation of random number sequence: a computer-generated random number sequence.

Rumiris 2006 *(Continued)*

	Randomisation and allocation concealment: central allocation (randomisation by an independent third party who had no conflict of interest in the study). Blinding of outcome assessment: treatment allocations were blinded to both the investigator and the patient until the study was finished. Documentation of exclusion: none reported. Use of placebo control: no, comparisons were between antioxidants versus iron and folic acid.
Participants	60 women between 8 and 12 weeks' gestation were eligible for randomisation (supplementation group: n = 29; folic acid group: n = 31). Setting: at the antenatal clinic of the Department of Obstetrics and Gynecology, University of Indonesia between March 2003 and June 2004. Eligibility criteria: pregnant women with low antioxidant status. Exclusion criteria: 1. history or current use of anti-hypertensive medication or diuretics; 2. use of vitamins C > 150 mg and/or E > 75 IU per day; 3. known placental abnormalities; 4. current pregnancy as a result of in vitro fertilisation; 5. regular use of platelet active drugs or non-steroidal anti-inflammatory drugs; 6. known fetal abnormalities; 7. documented uterine bleeding within a week of screening; 8. uterine malformations; 9. history of medical complications.
Interventions	Supplementation group: received antioxidant supplements daily - vitamins A (1000 IU), B6 (2.2 mg), B12 (2.2 mcg), C (200 mg), E (400 IU), folic acid (400 mcg), *N*-acetylcysteine (200 mg), Cu (2 mg), Zn (15 mg), Mn (0.5 mg), Fe (30 mg), calcium (800 mg), and selenium (100 mcg). Folic acid group: received Fe 30 mg and folic acid 400 mcg daily. Timing of the intervention: early pregnancy (8 to 12 weeks).
Outcomes	1. Pre-eclampsia. 2. Abortion. 3. Hypertension. 4. Intrauterine growth restriction. 5. Intrauterine fetal death.
Notes	Women's risk of spontaneous and recurrent miscarriage was unclear. Participating women had low antioxidant status at enrolment, as defined as superoxide dismutase level below 164U/mL. No nutritional information provided. Intention-to-treat analyses performed. Compliance: unclear, no information reported. Location: Indonesia. Timeframe: March 2003 and June 2004.

Risk of bias

Bias	Authors' judgement	Support for judgement

Rumiris 2006 *(Continued)*

Random sequence generation (selection bias)	Low risk	Computer-generated random number sequence.
Allocation concealment (selection bias)	Low risk	Central allocation (randomisation by an independent third party who had no conflict of interest in the study).
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Treatment allocations were blinded to both the investigator and the patient until the study was finished.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Authors claim the study had a double-blind design, but it is unclear if the assessors were blinded. Treatment allocations were blinded to both the investigator and the patient until the study was finished.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing data.
Selective reporting (reporting bias)	Low risk	All pre-specified outcomes were reported, no apparent evidence of selective reporting.
Other bias	Unclear risk	At baseline, the control group appears to have a 2 mmHg higher systolic blood pressure than the intervention group, this figure was of borderline statistical significance, P = 0.059.

Rush 1980

Methods	Randomisation and allocation concealment: unclear, women were allocated to groups based on "random assignment". Randomisation was stratified on pre-pregnancy weight, weight gain during pregnancy, previous low birthweight infant and protein intake. No other methodological details given. Blinding of outcome assessment: unclear, women were allocated to 2 forms of treatment or control, where both treatments were given as a canned beverage and the control group were given standard oral multivitamins. No information is given on blinding of outcome assessors. Documentation of exclusion: 237 women (22%) were excluded. Use of placebo control: no placebo, the control group received standard prenatal multivitamin supplements.
Participants	1051 women were recruited into the study. Women eligible were black, English speaking, and not greater than 30 weeks' gestation. They also had 1 of the following criteria: low pre-pregnant weight (under 110 pounds at conception); low weight gain at the time of recruitment; at least 1 previous low birthweight infant; a history of protein intake of less than 50 g in the 24 hours preceding recruitment. Women were not eligible if they were known to be seeking a termination, had specific chronic health disorders, if they admitted to recent use of narcotics or heavy use of alcohol, or weighed >= 140 pounds at conception. The mean gestation at enrolment ranged from 16-18 weeks for the treatment groups. 1225 women were invited to join the study, of which 1051 (84%) consented. Of these, 237 (22%) were excluded and 814 women (77%) remained active in the study until delivery and were allocated to 1 of 3 groups: supplement (n = 263), complement (n = 272) or control (n = 279).
Interventions	Women were randomised to 1 of 3 groups: 1. high protein supplement (daily 40 g animal protein, 470 calories, 1000 mg calcium, 100 mg magnesium, 60 mg iron, 4 mg zinc, 2 mg copper, 150 mcg iodine, 6000 IU vitamin A, 400 IU vitamin D, 30 USPU

Rush 1980 *(Continued)*

vitamin E, 60 mg vitamin C, 3 mg vitamin B1, 15 mg vitamin B2, 15 mg niacin, 2.5 mg vitamin B6, 1 mg pantothenic acid, 200 mcg biotin, 350 mcg folic acid, 8 mcg vitamin B12);

2. balanced protein-energy complement (6 g animal protein, 250 mg calcium, 12 mg magnesium, 40 mg iron, 0.084 mg zinc, 0.15 mg copper, 100 mcg iodine, 4000 IU vitamin A, 400 IU vitamin D, 60 mg vitamin C, 3 mg vitamin B1, 15 mg vitamin B2, 10 mg niacin, 3 mg vitamin B6, 1 mg pantothenic acid, 350 mcg folic acid, 3 mcg vitamin B12);
3. control (250 mg calcium, 0.15 mg magnesium, 117 mg iron, 0.85 mg zinc, 0.15 mg copper, 100 mcg iodine, 4000 IU vitamin A, 400 IU vitamin D, 60 mg vitamin C, 3 mg vitamin B1, 2 mg vitamin B2, 10 mg niacin, 3 mg vitamin B6, 1 mg pantothenic acid, 350 mcg folic acid, 3 mcg vitamin B12).

Women received the high protein or balanced protein-energy supplements in the format of a drink. Women in the control group received a standard oral prenatal multivitamin supplement.

Outcomes	1. Total weight gain, average weight gain and early weight gain during pregnancy. 2. Duration of gestation (presented as cumulative rates of delivery from life tables for each treatment group). 3. Preterm birth < 37 weeks. 4. Fetal death (before < 20 weeks' gestation and >= 20 weeks' gestation). 5. Neonatal death (according to gestation at delivery). 6. Birthweight (mean). 7. Somatic measures of infant growth at 1 year of age. 8. Psychological measures at 1 year of age.
Notes	Women's risk of spontaneous and recurrent miscarriage is unclear, as there is no information about concurrent medical conditions or other risk factors for miscarriage. Women in the trial had a low caloric intake at trial entry, and unexpectedly, an adequate protein intake. No other specific nutritional information is reported. Sample-size calculation reported: 250 women were required in each treatment group to show a 125 g difference in birthweight. A 25% loss to follow-up was incorporated into the sample size. Intention-to-treat analyses not performed. There were 9 sets of twins amongst the 3 treatment groups. Compliance: "on average, about three quarters of the prescribed amount of beverage was probably ingested". Location: New York City, USA. Timeframe: 1969 to 1976.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No methodological details given beyond reporting of 'random assignment'.
Allocation concealment (selection bias)	Unclear risk	No methodological details given beyond reporting of 'random assignment'.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No information provided about blinding of participants and personnel. Unlikely as participants were given canned beverages or multivitamins.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No information provided about blinding of outcome assessment.
Incomplete outcome data (attrition bias)	Unclear risk	237 women (22%) excluded, no intention-to-treat analysis.

Rush 1980 *(Continued)*

All outcomes

Selective reporting (reporting bias)	Unclear risk	Unclear if all pre-specified outcomes reported.
Other bias	Unclear risk	Limited methodological details provided.

Schmidt 2001

Methods	Randomisation and allocation concealment: unclear, women were "randomly assigned on an individual basis, to double-blind, weekly supplementation until delivery". Blinding of outcome assessment: unclear, double-blind stated in text but no details given. Documentation of exclusion: 42 women (17%) were lost to follow-up and excluded. Use of placebo control: control tablets containing iron and folic acid were given.
Participants	243 women were recruited into this study. Pregnant women between 16 and 20 weeks' gestation, aged between 17 and 35 years old, with a parity < 6 and Hb level between 80-140 g/L, were eligible for this study. Women were randomised to receive either vitamin A plus iron and folic acid (n = 122) or iron and folic acid only (n = 121). Of these 22 (18%) and 20 (17%) women in vitamin A plus iron and folic acid and the iron and folic acid groups respectively, dropped out between enrolment and the follow-up at 4 months.
Interventions	Women were randomised to a weekly supplementation with 120 mg ferrous sulfate and 500 mcg folic acid, with or without vitamin A (2400 retinol equivalents). Women were asked to take the trial tablets from between 16 and 20 weeks' gestation until birth.
Outcomes	1. Stillbirth. 2. Concentrations of Hb, serum ferritin and serum transferrin receptors, at or near term. 3. Concentrations of iron and vitamin A in breast milk. 4. Hb and serum vitamin A concentrations in the mother and infant at 4 months postpartum. 5. General health, growth and development measures in the first year of life.
Notes	Women risk status for spontaneous and recurrent miscarriage is unclear. At baseline, between 13% and 17% of women had marginal vitamin A deficiency 44% to 50% of women were anaemic. Sample-size calculation performed allowing for a 50% drop-out during the study period. Intention-to-treat analyses were not performed. Compliance: adherence to the tablet intake was assessed through interview during a postnatal home visit, which revealed that the median tablet intake was 50 tablets (i.e. 25 weeks), while only 17% of the subjects took more than 90 tablets. Location: Indonesia. Serial publications of this data report different denominators. Time frame: November 1997 to May 1998.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No information provided about sequence generation.
Allocation concealment (selection bias)	Unclear risk	Women were 'randomly assigned on an individual basis' but no other details given.

Schmidt 2001 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Double-blind used in the text but no details provided.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Authors claim the study had double-blind design, but it is unclear who were blinded. No further information was available.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	42 women (17%) were lost to follow-up and excluded, no intention-to-treat analyses performed.
Selective reporting (reporting bias)	Unclear risk	Serial publications of this study report different denominators.
Other bias	Unclear risk	Limited methodological details provided.

Spinnato 2007

Methods	Generation of random number sequence: the randomisation sequence was constructed by the data co-ordinating centre (DCC) as permuted blocks of random size, stratified by clinical centre, and implemented via a program residing on the clinical centres study computer. Randomisation and allocation concealment: central allocation. Blinding of outcome assessment: all clinicians and clinical investigators were blinded to group assignment. Documentation of exclusion: none reported. Use of placebo control: placebo control.
Participants	739 eligible women between $12^{0/7}$ and $19^{6/7}$ weeks of gestation were enrolled in the study (treatment: 371; placebo: 368). Setting: 4 Brazilian clinical centres: 1 primary clinical centre (Recife) and 3 additional clinical sites (Campinas, Botucatu, and Porto Alegre); each site's major teaching hospital serves a primarily urban low-income population. Eligibility criteria: women between $12^{0/7}$ and $19^{6/7}$ weeks of gestation and diagnosed with nonproteinuric chronic hypertension or a prior history of pre-eclampsia in their most recent pregnancy that progressed beyond 20 weeks' gestation. Exclusion criteria:multifetal gestation, allergy to vitamin C or vitamin E, requirement for aspirin or anticoagulant medication, 24-hour urinary protein ≥ 300 mg, pre-pregnancy diabetes mellitus, known fetal anomaly incompatible with life. Loss to follow-up: 32 women (treatment 16; placebo 16).
Interventions	Intervention group: daily treatment with both vitamin C (1000 mg) and E (400 IU) until delivery or until the diagnosis of pre-eclampsia. Control group: daily placebo until delivery or until the diagnosis of pre-eclampsia. Timing of the intervention: between $12^{0/7}$ and $19^{6/7}$ weeks of gestation.
Outcomes	1. Pre-eclampsia (women were followed through the 14th day postpartum for the occurrence of pre-eclampsia).

Spinnato 2007 *(Continued)*

2. Severity of pre-eclampsia.
3. Gestational hypertension.
4. Abruptio placentae.
5. Premature rupture of membranes.
6. Preterm birth.
7. Small-for-gestational age.
8. Low birthweight infant.

Notes	25 inclusion/exclusion criteria violations (23 enrolled outside 12-19 weeks' gestation; 2 twin gestations - 1 lost to spontaneous abortions, 1 delivered liveborn in treatment group); all 25 women remained in their assigned study groups. 26 women had early treatment terminations (treatment 19; placebo 7), but remained in follow-up. Women's risk of spontaneous and recurrent miscarriage was unclear. Women's nutritional status is also unclear. Intention-to-treat analyses performed. Compliance: average compliance was 85%, and similar between treatment groups. Location: Brazil. Timeframe: July 2, 2003 and November 23, 2006.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated sequence number.
Allocation concealment (selection bias)	Low risk	Central allocation.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	All clinicians and clinical investigators were blinded to group assignment.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Authors claim the study had double-blind design, but it is unclear who was blinded. No further information was available.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Small numbers of missing data, balanced across groups (32 women; treatment 16; placebo 16).
Selective reporting (reporting bias)	Low risk	All pre-specified outcomes were reported, no apparent evidence of selective reporting.
Other bias	Low risk	The study appears to be free of other sources of bias.

Steyn 2003

Methods	Randomisation and allocation concealment: "randomisation was undertaken by computer-generated numbers". Roche Pharmaceutical supplied numbered containers with either vitamin C or matching placebo, and they retained the study code until completion of the study. No other methodological details given. Blinding of outcome assessment: "double blind" stated, Roche Pharmaceuticals retained the code until completion of the study. Documentation of exclusion: none reported. Use of placebo control: placebo control.
Participants	200 women were recruited into the study. Women with a history of a previous mid-trimester abortion (defined as spontaneous expulsion of the uterine contents between 13 and 26 weeks' gestational age), or previous preterm labour, and less than 26 weeks' gestation were eligible and invited to participate. Women with iatrogenic causes of their previous preterm labour such as previous induction of labour before term for severe pre-eclampsia, were excluded. 203 consecutive women were approached, of which 200 (98.5%) consented and were randomised to either vitamin C (n = 100) or placebo (n = 100). No losses to follow-up were reported.
Interventions	Twice daily tablet of either 250 mg vitamin C or placebo, from trial entry until 34 weeks' gestation. All women were tested for bacterial vaginosis and all women with positive cultures for *Mycoplasma hominis* (and between 22 and 32 weeks' gestation) were treated with erythromycin for 7 days.
Outcomes	1. Preterm labour, defined as spontaneous onset of labour and delivery before 37 completed weeks. 2. The secondary outcome was perinatal outcome, a composite endpoint including birthweight, gestational age at delivery, perinatal mortality, duration of admission in the neonatal intensive care unit and neonatal complications. The age of fetal viability was considered to be 28 weeks' gestation.
Notes	Results are from an interim analysis performed when 100 participants were recruited into each arm. Recruitment was stopped after the interim analysis revealed few differences between the 2 groups. Unclear if there was a sample-size calculation performed. Women's risk profile spontaneous and recurrent miscarriage is unclear, although they are clearly at high risk of preterm birth. It is also unclear if multiple births were included. 6% of women had an inadequate dietary intake of vitamin C, defined as an intake < 67% of the recommended dietary allowance (70 mg per day). Compliance: women were requested to bring the containers to each visit and the remaining tablets were counted to improve and control compliance; however, no compliance data were reported. Country: South Africa. Timeframe: unclear.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated sequence number.
Allocation concealment (selection bias)	Low risk	Roche pharmaceuticals supplied numbered study containers and kept the study code until completion of the study.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Authors claim the study had double-blind design, but it is unclear who was blinded. Allocation was double-blind and Roche Pharmaceuticals retained the code until completion of the study.

Steyn 2003 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Authors claim the study had double-blind design, but it is unclear who was blinded. allocation was double-blind and Roche Pharmaceuticals retained the code until completion of the study.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No losses to follow-up reported.
Selective reporting (reporting bias)	Unclear risk	Recruitment stopped after an interim analysis.
Other bias	High risk	Results are from an interim analysis performed when 100 participants were recruited into each arm.

Summit 2008

Methods	Generation of random number sequence: computer-generated number; 262 clustered unit of randomisation (all pregnant women served by the same midwife received supplements with the same midwife identification number). Randomisation and allocation concealment: central allocation. Blinding of outcome assessment: all study scientists and personnel, government staff, and enrollees were unaware of the allocation. Documentation of exclusion: 1748 loss to follow-up before delivery (IFA: 853; MMN: 895); 1128 loss to follow-up after delivery (IFA: 553; MMN: 575). 10,549 pregnant women excluded post-randomisation because of trial termination (IFA group: 5057; MMN group: 5492). Use of placebo control: no placebo, comparisons were between multiple micronutrients and iron and folic acid.
Participants	41,839 pregnant women of any gestational age living on Lombok, Nusa Tenggara Barat Province, Indonesia. Women were allocated to IFA (n = 20,543) or MMN (n = 21,296).
Interventions	MMN group: the MMN was the UNIMMAP formulation containing 30 mg iron (ferrous fumarate) and 400 mcg folic acid along with 800 mcg retinol (retinyl acetate), 200 IU vitamin D (ergocalciferol), 10 mg vitamin E (alpha tocopherol acetate), 70 mg ascorbic acid, 1.4 mg vitamin B1 (thiamine mononitrate), 18 mg niacin (niacinanide), 1.9 mg vitamin B6 (pyridoxine), 2.6 mcg vitamin B12 (cyanocobalamin), 15 mg zinc (zinc gluconate), 2 mg copper, 65 mcg selenium, and 150 mcg iodine - 1 capsule daily up to 3 months after birth. IFA group: the IFA contained 30 mg iron (ferrous fumarate) and 400 mcg folic acid - 1 capsule daily up to 3 months after birth. Timing of the intervention: any time during pregnancy.
Outcomes	1. Early infant mortality (deaths until 90 days postpartum). 2. Neonatal mortality. 3. Fetal loss (abortions and stillbirths). 4. Low birthweight.
Notes	Women's risk of spontaneous and recurrent miscarriage was unclear. Women's nutritional status is also unclear. However, 30% of women in each group had an mid upper arm circumference < 23.5cm, which was used as an indicator of women being undernourished. Intention-to-treat analyses performed.

Summit 2008 *(Continued)*

Compliance: median compliance was 85%, there was no difference between treatment groups in compliance.

Location: Indonesia.

Timeframe: July 1, 2001 to April 1, 2004.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated number.
Allocation concealment (selection bias)	Low risk	Central allocation.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	All study scientists and personnel, government staff, and enrollees were unaware of the allocation.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	The code to indicate which strip was IFA or MMN was known only by the manufacturing production manager and a quality control officer from UNICEF. All study scientists and personnel. government staff, were unaware of the allocation. Blinding is unlikely to be broken.
Incomplete outcome data (attrition bias) All outcomes	High risk	Loss to follow-up: 1748 loss to follow-up before delivery (IFA: 853; MMN: 895); 1128 loss to follow-up after delivery (IFA: 553; MMN: 575). Post-randomisation exclusion: 10,549 pregnant women excluded because of trial termination (IFA group: 5057; MMN group: 5492).
Selective reporting (reporting bias)	Low risk	All pre-specified outcomes were reported, no apparent evidence of selective reporting.
Other bias	Low risk	The study appears to be free of other sources of bias.

Sunawang 2009

Methods	Randomisation and allocation concealment: 160 clusters were randomly assigned to 4 blocks of 40 clusters each. 2 of the 4 blocks received either MMN of IFA. No details of how blocks were selected. 432 women in 40 clusters were allocated to the group receiving multiple micronutrients and 411 in the other 40 clusters were allocated to the iron–folic acid group. No further details on how allocation was done. Blinding of outcome assessment: single-blind design, no further details provided. Documentation of exclusion: 93 women (11%) were excluded. Use of placebo control: no placebo, the control group received iron-folic acid supplementation.
Participants	843 women residing in Indramayu District in the West Java Province of Indonesia who were between 12 to 20 weeks of gestation. Only women intending to remain in the study location until giving birth were recruited. Women suffering from potentially confounding illnesses, including diabetes, coronary heart disease, and tuberculosis, were excluded from the study.

Sunawang 2009 *(Continued)*

Interventions	MMN supplements containing 15 micronutrients vs IFA (60 mg of elemental iron as ferrous sulfate and 0.25 mg of folic acid). Supplementation was from time of enrolment at 12 to 20 weeks of gestation and continued to 30 days postpartum.
Outcomes	1. Birthweight. 2. Anthropometry. 3. Hb, serum ferritin, serum zinc, and serum retinol. 4. Compliance. 5. Side effects of supplementation. 6. Morbidity. 7. Fetal loss.
Notes	Women's risk of spontaneous and recurrent miscarriage is unclear. Women's nutritional status is also unclear. Sample size calculation not done. Intention-to-treat analysis performed. Compliance: Data on compliance was collected from weekly visits. Mean adherence in the intervention group 68% and control group 71%. Location: Indonesia. Timeframe: May 2001 to December 2002.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	160 clusters were randomly assigned to 4 blocks of 40 clusters each. 2 of the 4 blocks received either MMN of IFA. No details of how blocks were selected. pg s489 pgh 5.
Allocation concealment (selection bias)	Unclear risk	432 women in 40 clusters were allocated to the group receiving multiple micronutrients and 411 in the other 40 clusters were allocated to the iron–folic acid group. No further details on how allocation was done. pg s489, pgh 7.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Authors claim the study had a single-blind design, but it is unclear who was blinded. Probably not done. pg s489 pgh 8.
Blinding of outcome assessment (detection bias) All outcomes	High risk	No details of blinded outcome assessment provided.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	23/432 missing in MMN and 33/411 missing in IFA. Reasons for drop-out are similar, but IFA had 5 twin births while MMN cluster had none. Fig. 1.
Selective reporting (reporting bias)	Low risk	All pre-specified outcomes were reported as described.
Other bias	Low risk	The study appears to be free of other sources of bias.

Tofail 2008

Methods	Generation of random number sequence: a computer-generated register was used for randomisation. Randomisation was performed in blocks of 12 food supplementation was randomly allocated but not blinded. micronutrient capsules looked identical and women were allocated to 1 of 3 types of micronutrient supplements in a 2 by 3 design. Blinding of outcome assessment: allocation code was not broken until after the analysis. Documentation of exclusion: 845 losses to follow-up (19%). Use of placebo control: no placebo, the control group received IFA (Fe30Fol) supplementation.
Participants	4436 pregnant women from rural Bangladesh within 6-8 weeks of conception (not more than 14 weeks). Women with Hb < 80 g/L were ineligible for participation.
Interventions	MMNs containing 15 recommended micronutrients (30 mg of iron, 400 µg of folic acid). The micronutrient supplements were offered to the enrolled pregnant women at the 14weeks' clinic visit up to 3 months after delivery. Intervention was divided into early or late food supplementation. Early or usual food supplementation plus 1, 2 or 3: 1) 30 mg iron(fumarate) + 400 mcg folic acid (Fe30Fol) 2) 60 mg iron (fumarate) + 400 mcg folic acid (Fe60Fol) 3) 30 mg iron (fumarate), 400 mcg folic acid, 800 mcg RE vitamin A (retinyl acetate), 5 mcg vitamin D (cholecalciferol), 10 mg vitamin E (a-tocopherol acetate), 70 mg vitamin C, 1.4 mg thiamine (mononitrate), 1.4 mg riboflavin, 18 mg niacin, 1.9 mg vitamin B-6 (pyridoxine hydrochloride), 2.6 mcg vitamin B-12 (cyanocobalamin), 15 mg zinc (sulfate), 2 mg copper (sulfate), 65 mcg selenium (sodium selenite), and 150 mcg iodine (potassium iodide) (MMNs). All women received food supplement which consisted of roasted rice powder, roasted pulse powder, molasses, and soybean oil and had a total energy content of 2500 kJ. Early (immediately after detection of pregnancy, around 9 weeks) enrolment in food supplementation or usual (at the time of their choosing, around 20 weeks).
Outcomes	Infant outcomes: 1. Blood Hb and plasma ferritin, zinc, retinol, vitamin B-12, and folate at 6 months. 2. Low birthweight. 3. Small-for-gestational age. 4. Morbidities (diarrhoea, lower acute respiratory infections). 5. Birth anthropometry. 6. Neonatal survival. 7. Blood pressure. 8. Kidney function 9. Child growth and body composition. Maternal outcome: 1. Hb at 30 weeks.
Notes	Women's risk of spontaneous and recurrent miscarriage was unclear. Women's nutritional status is also unclear. Sample size calculation: not done. Intention-to-treat analysis performed.

Tofail 2008 *(Continued)*

Compliance: the number of micronutrient pills taken in the first 30 weeks of pregnancy was 79+/-34 in the Fe30 group, 78+/-34 in the Fe60 group, and 75+/-33 in the MM group.

Location: Bangladesh.

Timeframe: November 2001 to June 2006.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	A computerised tracking system assigned women to 1 of the 6 groups in blocks of 12 women were randomly allocated. "Computer generated register of study identity numbers with random assignment of food groups (“E” or “U”) and micronutrient groups (from 12 possible pill bottle number codes) was used for randomization.” Randomisation was probably done. Eneroth 2011 pg 221.
Allocation concealment (selection bias)	Low risk	Micronutrient capsules looked identical.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Each micronutrient group had been given 4 different number codes to decrease the risk of unblinding. Pg 2054.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Randomisation codes were safely kept at the administrative office of ICDDR,B and were not broken until after performing the intention-to-treat analyses. Pg 2054.
Incomplete outcome data (attrition bias) All outcomes	Low risk	845 of 4436 losses to follow-up (19%) before birth; reasons were available. Numbers of women lost to follow-up did not differ among the treatment groups.
Selective reporting (reporting bias)	Low risk	All the study's pre-specified outcomes have been reported.
Other bias	Low risk	The study appears to be free of other sources of bias.

Van den Broek 2006

Methods	Generation of random number sequence: using a random-generation procedure. Randomisation and allocation concealment: the supplements in vitamin A and placebo treatments allocated were prepared in identical capsules and were packaged in bottles according to the randomisation schedule (sealed envelopes) by midwives who were not involved in the trial conduct. Blinding of outcome assessment: neither the women nor the midwives involved in treatment allocation revealed the randomisation schedule to anyone involved in the conduct of the trial. Documentation of exclusion: 77 loss to follow-up before assessment at 26-28 weeks (5000 IU vitamin A: 26; 10,000 IU vitamin A: 26; placebo: 25). Additional 93 loss to follow-up before assessment at 36-38 weeks (5000 IU vitamin A: 34; 10,000 IU vitamin A: 28; placebo: 31). Use of placebo control: placebo control.
Participants	700 women with singleton pregnancies at 12-24 weeks' gestation measured by ultrasound scan (5000 IU vitamin A: 234; 10,000 IU vitamin A: 234; placebo: 232).

Van den Broek 2006 *(Continued)*

	Setting: the antenatal clinic at the Namitambo rural Health Centre in southern Malawi, central Africa. Eligibility criteria: (Hb) < 11.0 g/dL by HemoCue screening method at first antenatal visit, singleton pregnancy with gestational age > 12 weeks and ≤ 24 weeks measured by ultrasound scan, no fetal abnormality detectable by ultrasound at time of booking, residing in the catchment area of the health centre. Exclusion criteria: women > 24 weeks' gestation, or twin pregnancy.
Interventions	• Intervention group 1: 5000 IU vitamin A daily until delivery. • Intervention group 2: 10,000 IU vitamin A daily until delivery. • Comparison group: placebo daily until delivery. Timing of the intervention: supplementation started as early as possible after 12 weeks of pregnancy. All women received iron tablets daily (60 mg elemental iron as ferrous sulphate with 0.25 mg folic acid).
Outcomes	1. Anaemia status (no anaemia ([Hb] ≥ 11.0 g/dL), anaemia ([Hb] < 11.0 g/dL) or severe anaemia ([Hb] < 8.0 g/dL). 2. Hb concentration (Coulter counter value), iron status (determined by serum ferritin and serum transferring receptor concentration). 3. Evidence of infection (assessed by serum CRP, peripheral malaria parasitaemia and HIV status). 4. Vitamin A status (determined by serum retinol and the MRDR).
Notes	Women's risk of spontaneous and recurrent miscarriage was unclear. Women's nutritional status is also unclear. Intention-to-treat analyses performed. Compliance: unclear, no information provided. Location: Malawi. Timeframe: April 1997 and July 1999.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Random-generation procedure used.
Allocation concealment (selection bias)	Low risk	The vitamin A and placebo treatments allocated were prepared in identical capsules and packaged in bottles according to the randomisation schedule (sealed envelopes) by midwives who were not involved in the trial conduct.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Neither the women nor the midwives involved in treatment allocation revealed the randomisation schedule to anyone involved in the conduct of the trial.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No information provided about blinding of outcome assessment.
Incomplete outcome data (attrition bias) All outcomes	High risk	77 loss to follow-up before assessment at 26-28 weeks (5000 IU vitamin A: 26; 10,000 IU vitamin A: 26; placebo: 25). Additional 93 loss to follow-up before assessment at 36-38 weeks (5000 IU vitamin A: 34; 10,000 IU vitamin A: 28; placebo: 31).

Van den Broek 2006 *(Continued)*

Selective reporting (reporting bias)	Low risk	All pre-specified outcomes were reported, no apparent evidence of selective reporting.
Other bias	Low risk	The study appears to be free of other sources of bias.

Villar 2009

Methods	Generation of random number sequence: no sequence generation details available. Randomisation and allocation concealment: central allocation (randomisation was performed by the statisticians of the British VIP Trial). Blinding of outcome assessment: "double blind" stated. Documentation of exclusion: 10 women (treatment 6; placebo 4), and 29 infants (treatment 13, placebo 16) were lost to follow-up. Use of placebo control: placebo control.
Participants	1365 women between 14-22 gestational age agreed to participate and were randomised (vitamins group: 687; placebo group: 678). Setting: antenatal clinics located in Nagpur, India; Lima and Trujillo, Peru; Cape Town, South Africa; and Ho Chi Minh City, Viet Nam which served populations with low social-economic status and had evidence of overall low nutritional status, between October 2004 and December 2006. Eligibility criteria: pregnant women considered high risk for pre-eclampsia (chronic hypertension, renal disease, pre-eclampsia-eclampsia in the pregnancy preceding the index pregnancy requiring delivery before 37 weeks' gestation, HELLP syndrome in any previous pregnancy, pre-gestational diabetes, primiparous with a BMI > 30 kg/m^2, history of medically-indicated preterm delivery, abnormal uterine artery Doppler waveforms and women with antiphospholipid syndrome), multifetal gestation. Women ingesting medications with aspirin-like compounds were not excluded. Exclusion criteria: women ingesting vitamin supplements that contained ≥ 200 mg of vitamin C and/or ≥ 50 IU of vitamin E and women receiving warfarin.
Interventions	Intervention group: received 1000 mg vitamin C and 400 IU of vitamin E daily until delivery. Comparison group: received placebo daily until delivery. Timing of the intervention: between 14 and 22 weeks' gestation.
Outcomes	1. Pre-eclampsia. 2. Eclampsia. 3. Placental abruption. 4. Low birthweight (< 2500 g). 5. Small-for-gestational age (< 10th centile of the WHO recommended standard). 6. Intrauterine or neonatal death before hospital discharge. 7. Preterm delivery (< 37 weeks). 8. Early preterm delivery (< 34 weeks). 9. Very low birthweight (< 1500 g). 10.≥ 7 days in the neonatal intensive care unit. 11.Congenital malformations. Pre-eclampsia information was unavailable for 14 women in the vitamins and 9 in the placebo group.

Villar 2009 *(Continued)*

	There were data from 81 supplemented (11.8%) and 100 placebo-treated (14.7%) women with multiple pregnancies, for whom newborn outcomes were considered separately.
Notes	Women's risk of spontaneous and recurrent miscarriage was unclear. Women at high risk of pre-eclampsia were included but data on fetal loss was not reported separately for this group. No specific information on women's nutritional status is included; however, the paper states that the trial was conducted in populations with 'documented low nutritional status'. Intention-to-treat analyses performed. Compliance: median compliance was 87%, and was similar between the treatment groups. Location: Antenatal clinics in India, Peru, South Africa and Vietnam. Timeframe: October 2004 and December 2006.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation sequence blocked by centre in groups of 2 to 10 individuals.
Allocation concealment (selection bias)	Low risk	Central allocation (randomisation was performed by the statisticians of the British VIP Trial).
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Women and investigators blinded to allocation.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Identifying characteristics and randomisation code were kept in a secure and separate database in the server unavailable to the research team, until all data analyses were completed.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Small numbers of missing data, balanced across groups. Women: 10 (treatment 6; placebo 4). Infants: 29 (treatment 13; placebo 16).
Selective reporting (reporting bias)	Unclear risk	Perinatal death was reported instead of pre-specified neonatal death.
Other bias	Low risk	The study appears to be free of other sources of bias.

West 2011

Methods	Generation of random number sequence: sectors were used as the unit of randomisations for supplement allocation, 3 sets of 3 identical coins on which the numbers 1, 2 or 3 were written were placed into a container, mixed and removed randomly, without replacement, and the 3-digit code of each sector was read aloud sequentially. Study supplements were identical in colour, taste and external appearance. Treatment codes were assigned by the Nutrilite Health Institute and were kept in a sealed envelope in a locked cabinet at both Nutrilite and Johns Hopkins University. Masking was further ensured by having a senior administrative staff (not involved in field activities) recode the supplement bottles with sector-specific permanent stickers bearing codes from 001 to 596.

West 2011 *(Continued)*

	Blinding of outcome assessment: investigators were all blinded to the allocation codes until the end of the parent trial. Documentation of exclusion: 628 women (1%) were excluded. Use of placebo control: placebo control.
Participants	102,769 women from 596 sectors (60,294 pregnancy identified and 59,666 pregnancies included) 19 rural unions in the northwest Districts of Gaibandha and Rangpur in rural Bangladesh. Women were recruited from the first trimester of pregnancy through 12 weeks (84th day) after pregnancy termination. Eligible women included pregnant or postpartum, lactationally amenorrhoeic women were placed on a 'waiting list', and only became eligible for pregnancy surveillance once their menses resumed. Married women, women entering the study area within 4 months of marriage were also eligible to join the cohort under pregnancy surveillance. And when identified as pregnant, enrolled. Women who never got pregnant during the study period, permanently moved from the study area, were sterilised, reported menopause, divorce or death of husband, refused to participate or participation status unknown, died before detecting a pregnancy , had a pregnancy outcome after October 12, 2006, reported a last menstrual period after January 5, 2006 or had an unknown date of a last menstrual cycle were excluded.
Interventions	1. Vitamin A (consisting of 7000 mcg retinol equivalents, or 23,300 IU, of VA palmitate in soybean oil with a small amount of vitamin E as an antioxidant). 2. β-carotene at 42 mg—an amount equivalent to 7000 mcg REs administered weekly from the time of pregnancy enrolment until 3 months postpartum. 3. Control group received placebo (consisting of soybean oil with a small amount of vitamin E as an antioxidant). All 3 supplements contained 5 IU vitamin E in oil.
Outcomes	1. All-cause pregnancy-related mortality. 2. Fetal loss due to miscarriage or stillbirth. 3. Infant mortality under 3 months of age. 4. Maternal obstetric and infectious morbidity. 5. Infant infectious morbidity. 6. Maternal and infant micronutrient status. 7. Fetal and infant growth. 8. Prematurity. 9. External birth defects. 10. Postnatal infant growth to 3 months of age.
Notes	Women's risk of spontaneous and recurrent miscarriage was unclear. Women's nutritional status: a 1-week history of diet at trial entry and 12 weeks after pregnancy was reported. Sample size estimation: based on a 35% or greater reduction in all-cause mortality. Primary outcomes were compared on an intent-to-treat basis. Compliance: adherence to supplementation was comparable across groups, with approximately 80% of women having directly consumed (under staff supervision) at least 64% of eligible supplements. Location: Bangladesh. Timeframe: August 2001 to January 2007.

Risk of bias

Bias	Authors' judgement	Support for judgement

West 2011 *(Continued)*

Random sequence generation (selection bias)	Low risk	Sectors were randomised in blocks of 9. 3 sets of 3 identical coins on which the numbers 1, 2 or 3 were written were placed into a container, mixed and removed randomly, without replacement, and the 3-digit code of each sector was read aloud sequentially. Pg 7 (Labrique).
Allocation concealment (selection bias)	Low risk	Study supplements were identical in colour, taste and external appearance. Supplements were originally shipped in identically-labelled, 100-count white opaque plastic bottles distinguished only by the code number-1, 2 or 3-listed on the label. A senior administrative staff (not involved in field activities) recode the supplement bottles with sector-specific permanent stickers bearing codes from 001 to 596. Treatment codes were assigned by the Nutrilite Health Institute and were kept in a sealed envelope in a locked cabinet at both Nutrilite and Johns Hopkins University. Pg 7-8 (Labrique).
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Study participants, interviewers, field supervisors and investigators remained masked to treatment assignments until the end of the trial. Pg 8 (Labrique).
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Investigators remained masked to treatment assignments until the end of the trial. Pg 8 (Labrique).
Incomplete outcome data (attrition bias) All outcomes	Low risk	Number of missing data among each group are small and balanced with detailed reason.
Selective reporting (reporting bias)	Low risk	Registration of trial and outcomes reported as described previously.
Other bias	Low risk	The study appears to be free of other sources of bias.

West 2014

Methods	Generation of random number sequence: 596 sectors of comparable size were used as units of randomisations. "We stratified the contiguous list of 596 sectors into 74 blocks of 8 each (for the first 592 sectors), plus a 75th block of 4 sectors. A sector-supplement code key with A or B was created by flip of a coin, reflecting assignment to iron–folic acid or MM supplementation, and duplicated, and each of 2 copies was sealed into an envelope by an uninvolved colleague at Johns Hopkins. Computer program randomised sectors within blocks to 1 of 2 codes such that each permutation had an equal probability of being chosen. The resulting 2 lists of sectors were securely transmitted to field headquarters. 1 envelope with the code key was securely transmitted to the supplement producer and the other sealed in an envelope and secured at Johns Hopkins. At no time during the trial did study investigators or field or data management staff have access to the key." Blinding of outcome assessment: outcome assessors were blinded to the treatment allocation. Documentation of exclusion: 1351 pregnant women (3%) were excluded. Use of placebo control: no placebo, the control group received IFA supplementation.
Participants	Participants in the study included 44,567 pregnant women and 28,518 infants in rural setting in Bangladesh. Pregnant women were recruited around ˜ 10 weeks' gestation. All women under 45 years of age who are married and living with their husbands as residents of the JiVitA study area at the time of an initial population enumeration, and those who enter the cohort as newlyweds, were eligible for pregnancy surveillance and, when identified as pregnant, enrolled. Women who permanently moved, were sterilised or menopausal, died, and did not get pregnant were excluded.

West 2014 *(Continued)*

Interventions	Weekly supplementation from enrolment (early pregnancy) to 3 months postpartum. Multiple-micronutrient: vitamin A (770 mcg retinol equivalents), vitamin D (5 mcg), vitamin E (15 mg), thiamin (1.4 mg), riboflavin (1.4 mg), niacin (1.4 mg), vitamin B12 (2.5 mg), vitamin B6 (1.9 mg), vitamin C (85 mg), zinc (12 mg), iodine (220 mcg), copper (1000 mcg), and selenium (60 mcg). The control group received IFA supplement (standard care).
Outcomes	1. Infant survival: determine the efficacy of a standard MMN supplement given to women daily during pregnancy through 12 weeks postpartum in lowering neonatal and infant mortality through 6 months of age by > 15% compared to the mortality of infants whose mothers receive daily iron + folic acid. 2. Fetal and newborn outcomes: assess the efficacy of the MM intervention in reducing the: a) stillbirth rate by 23% or more, from an expected 30 to 24 or fewer stillbirths per 1000 births (i.e. live + still births); b) rate of preterm birth (live birth delivered < 37 weeks' gestation) by 10% or more, from an expected 20% to 18% or fewer of all live births; c) prevalence of low birthweight (< 2500 g) by 5% or more, from an expected 40% to 38% or fewer of all live births; and d) neonatal morbidity related to sepsis, birth asphyxia, hypothermia and diarrhoea. 3. Other infant outcomes (to 6 months of age): assess the efficacy of the MM supplement intervention in improving: a) linear and ponderal growth, including its ability to protect lean body mass, that could lead to reduced prevalences of stunting, wasting and underweight status in infancy; b) infant morbidity, including diarrhoea and acute lower respiratory infection, in the first 3 months of life; c) micronutrient intake, represented by measured breast milk micronutrient concentrations; d) micronutrient status, and reducing prevalences of multiple deficiencies. 4. Maternal outcomes: assess the efficacy of either MM supplement intervention in influencing among mothers the: a) prevalence of infectious morbidity, based on history, testing and signs, during pregnancy and in the 1st 6 months postpartum; b) rates of potentially fatal ("near miss") obstetric complications.
Notes	Women's risk of spontaneous and recurrent miscarriage: previous fetal loss and infant death reported. Women's nutritional status is unclear. Sample size estimation: live-born infants based on a 15% or greater reduction in 6-month mortality; pregnancies based on a 30% loss from induced abortion, miscarriage, and stillbirth. Intent-to-treat analysis of all outcomes. Compliance: adherence was high, with half the women in both groups estimated to consume a median of approximately 95% of all distributed supplements; 80% in both groups consumed more than 80% of their intended tablets. Location: Bangladesh. Timeframe: 2008 to 2012.

Risk of bias

West 2014 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"We used an in-house program (VBScript, Microsoft) that recognized 70 possible permutations for n = 8 sectors and k = 2 supplement allocations and 6 for the last block of n = 4sectors. Using this program, we randomised sectors within blocks to 1 of 2 codes such that each permutation had an equal probability of being chosen". Pg 2650.
Allocation concealment (selection bias)	Low risk	"Supplements were identical in appearance. Tablets were packed into opaque plastic bottles, affixed with codes AorB representing supplement content, and shipped to the field where logistics staff, uninvolved in the study, relabeled bottles with sector numbers(001-596) according to the random allocation list." Pg 2652.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blinded and blinding of the participants is unlikely to have been broken.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	At no time during the trial did study investigators or field or data management staff have access to the key. Pg 2651.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Numbers of missing outcome data in both group are small and balanced with similar reasons. Pg 2651, fig 1.
Selective reporting (reporting bias)	Low risk	Study protocol was available and all of the study's pre-specified outcomes were reported in studies.
Other bias	Low risk	The study appears to be free of other sources of bias.

Wibowo 2012

Methods	Generation of random number sequence: participants were randomised according to a computer-generated random number sequence. "Participants were assigned on an individual basis to antioxidant or placebo supplementation and remained in the same allocation group throughout the pregnancy and 2 weeks postpartum." No details about how allocation concealment was done. Blinding of outcome assessment: unclear. Documentation of exclusion: 6 women (5.5%) were excluded. Use of placebo control: no placebo, the control group received non-antioxidant multiple micronutrients.
Participants	110 women residing in Cipto Mangunkusumo National Hospital, Jakarta, Indonesia between 8 and 12 weeks of gestation. To be eligible, women had to have normal blood pressure at their first visit in pregnancy and again at trial entry. Women with multiple pregnancy, fetal anomaly, thrombophilia, infections, mola hydatidosa, chronic renal failure, uncontrolled hypertension, placental abnormalities, documented uterine bleeding within a week of screening, uterine malformation and history of medical and metabolic complication, such as heart disease or diabetes were excluded.
Interventions	Antioxidant multiple micronutrient (MMN) supplement mixed into milk administered from trial entry until 2 weeks postpartum. Control received non-antioxidant (MMN) supplement and all women received 40 g of milk powder.

Wibowo 2012 *(Continued)*

Outcomes	1. Pre-eclampsia. 2. Fetal growth restriction. 3. HELLP syndrome. 4. Biochemical markers.
Notes	Women's risk of spontaneous and recurrent miscarriage: history of pre-eclampsia reported. Women's nutritional status is unclear. Sample size calculation: based on an expected incidence of pre-eclampsia in the control group of at least 29% and in the treatment group of at least 30%. Analyses were performed on an intention-to-treat basis. Compliance: unclear, no information reported. Location: Jakarta, Indonesia. Timeframe: June 2001 to December 2009.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Participants were "..randomized according to a computer-generated random number sequence" pg 1153, pgh 2.
Allocation concealment (selection bias)	Unclear risk	"Participants were assigned on an individual basis to antioxidant or placebo supplementation." No details of how allocation was done. pg 1153, pgh 2.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"Treatment allocations were blinded to both investigator and the patient..." pg 1153, pgh 2.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	"Investigators blinded to the sample background" but not sure if they blinded outcomes of interest in current review.
Incomplete outcome data (attrition bias) All outcomes	Low risk	3/52 drop-out from supplementation group and 3/58 drop-out from control group. drop-out rate balanced in both groups.
Selective reporting (reporting bias)	Low risk	Primary and secondary outcomes reported as planned in the protocol.
Other bias	Low risk	The study appears to be free of other sources of bias.

Xu 2010

Methods	Generation of random number sequence: double-blinded, multicentre trial. Randomisation was performed through an electronic data management platform, which enabled randomisation and data entry over the Internet. They were randomly allocated at a ratio of 1:1 to antioxidant supplementation (vitamins C and E) group or to placebo group through an electronic data management platform. Blinding of outcome assessment: outcome assessors were blinded to the treatment allocation.

Xu 2010 *(Continued)*

	Documentation of exclusion: 277 women (10.5%) were excluded. Use of placebo control: placebo control.
Participants	2460 women participated in the study. Women were eligible for the trial if they were between 12 and 18 completed weeks of pregnancy on the basis of last menstrual period and confirmed by early ultrasound examination. The exclusion criteria were: (1) women who regularly consumed supplements200 mg/day for vitamin C and/or 50 IU/day for vitamin E; (2) women who took warfarin; (3) women who had known fetal abnormalities, (4) women who had a history of medical complications, (5) women with repeated spontaneous abortion, (6) women who used an illicit drug during the current pregnancy.
Interventions	Women were provided either with vitamins C and E or placebo. Total daily dose of vitamin C was 1000 mg, and that of vitamin E was 400 IU.
Outcomes	Primary outcomes: 1. Gestational hypertension and its adverse conditions. Other maternal outcomes: 1. Death. 2. Severe gestational hypertension. 3. Severe pre-eclampsia. 4. Prelabour rupture of membranes (PROM). 5. Preterm PROM (PPROM). 6. Hospitalisation prior to giving birth. Fetal and neonatal outcomes: 1. Fetal loss or perinatal death (defined as any fetal loss at 20 weeks), 2. Stillbirth. 3. Neonatal death. 4. Preterm birth (before 37 weeks of gestational age; gestational age corrected by early ultrasound scan). 5. Preterm birth (before 34 weeks of gestational age. 6. Small for gestational age (defined as 5th or 10th centile). 7. Perinatal mortality. 8. Spontaneous abortion. 9. Neonatal morbidity indicators.
Notes	Women's risk of spontaneous and recurrent miscarriage: history of pre-eclampsia and gestational hypertension reported as well as obstetric history (abortion, stillbirth, low birthweight, preterm birth). Women's nutritional status: use of supplements reported . Sample size calculation: based on an expected 4% and 15% incidence of the primary outcome in the low- and high-risk strata, respectively. Analyses were performed on an intention-to-treat basis. Compliance: 85.5% in the vitamin group, 86.5% in the placebo group.

Xu 2010 *(Continued)*

Location: multicentre trial in Canada (17 centres) and Mexico (10 centres).

Timeframe: January 2004 to March 2006.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	They [women] were randomly allocated at a ratio of 1:1 to antioxidant supplementation (vitamins C and E) group or to placebo group through an electronic data management platform."Pg 239.e3
Allocation concealment (selection bias)	Unclear risk	Although paper states that "Women in the placebo group were advised to take capsules that were identical in appearance to the active treatment capsules", no details were provided on how they were allocated to treatment groups
Blinding of participants and personnel (performance bias) All outcomes	Low risk	None of the trial staff or any other person involved in the trial knew the treatment allocation for any women until after completion of the trial analysis." Pg 239.e3 and 4
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"None of the trial staff or any other person involved in the trial knew the treatment allocation for any women until after completion of the trial analysis."Pg 239.e4
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	A higher loss to follow-up was seen in the Mexican centres although the loss was balanced between treatment and placebo groups
Selective reporting (reporting bias)	Low risk	Outcomes reported according to the trial registration.
Other bias	Low risk	The study appears to be free of other sources of bias.

Zagre 2007

Methods	Generation of random number sequence: cluster-randomised study wherin villages-not individuals-were randomly assigned to 1 treatment group or the other. The 2 supplements looked different but a coding system was adopted. "…packaged the supplements in boxes with identical labelling except for the supplement code"… "the code letter did not distinguish which supplement was used". Blinding of outcome assessment: unclear if outcome assessors were unaware of participants' allocation to treatment or control group. Documentation of exclusion: 768 women (20.9%) were excluded. Use of placebo control: no placebo, the control group received iron-folic acid supplementation.
Participants	3670 women from Maradi, rural Niger. Women who lived in 1 of the selected villages and who had experienced amenorrhoea for less than 12 weeks were eligible for participation. Exclusion criteria included women with night blindness and/or clinical signs of severe anaemia.
Interventions	Daily multiple micronutrients consisting vitamin A 800 mcg,vitamin D 200 IU, vitamin E 10 mg, vitamin C 70 mg, vitamin B1 1.4 mg, vitamin B2 1.4 mg, vitamin B3 18 mg, vitamin B6 1.9, vitamin B12 2.6 mg, folic acid 400 mcg, iron 30 mg, zinc 15 mg, copper 2 mg, selenium 65 mcg, and iodine 150 mcg from enrolment until delivery. The control group received iron/folic acid.

Zagre 2007 *(Continued)*

Outcomes	Maternal outcomes: 1. Birth assistance. 2. Conditions of delivery. 3. Breastfeeding practices. 4. Miscarriage. 5. Stillbirths. 6. Maternal deaths. Infant outcome: 1. Birthweight.
Notes	Women's risk of spontaneous and recurrent miscarriage is unclear. Women's nutritional status is unclear. Sample size calculation: based on reduction of 25% in low birthweight. Intention-to-treat analysis not performed. Compliance: at subsequent visits, the remaining capsules were counted, and the number of missing capsules was replenished for another month and noted in the particular booklet. Compliance with treatment in the intervention group was 79.2% ± 18.1% and in the control group 78.4% ± 18.5%. Location: Maradi, Niger. Timeframe: January 2004 to March 2005.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"Villages-not individuals-were randomly assigned to one treatment group or the other." No details on how randomisation was done.
Allocation concealment (selection bias)	Low risk	"Packaged the supplements in boxes with identical labeling except for the supplement code."
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Health workers and midwives did not distinguish which supplement was used.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	"Data collectors were informed that each supplement came in two sizes and colors, so that the code letter did not distinguish which supplement was used."
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Proportion of women lost to follow-up was significantly different across groups 335/1777 in IFA and 290/L ,893 in MMN. Detailed reasons for missing data not provided.
Selective reporting (reporting bias)	Unclear risk	Many outcomes were assessed but report was limited to only 2 outcomes.
Other bias	High risk	There were differences in the baseline characteristics of participants. Women in control group tended to be poorer and less educated and more women in intervention group used more preventive measures against malaria and had larger households.

Zeng 2008

Methods	Generation of random number sequence: randomisation of villages was stratified by county with a fixed ratio of treatments (1:1:1) and blocking of 15. The randomisation schedule was generated off site with a pseudo-random number generator. Allocation concealment was described “a treatment colour code was assigned to each village based on the treatment allocation schedule. The treatment codes were opened only once all data had been collected”. Blinding of outcome assessment: unclear. Documentation of exclusion: 133 women (2.3%) were lost to follow-up, 279 women (4.8%) stopped taking the supplement and refused to continue to participate, and 601 women (10.3%) experienced fetal loss. Use of placebo control: no placebo, the control group received folic acid alone.
Participants	5828 women from Shaanxi Province of north west China between < 12 – 28 weeks' gestational age. Eligibility included all women resident in the counties who became pregnant between August 2002 and January 2006. Women were ineligible if they: 1. were already taking supplements; 2. had a serious illness; 3. had an abnormal reproductive history; 4. were planning; 5. to work outside the area; or were more than 28 weeks pregnant.
Interventions	Supplementation with MMN; IFA (60 mg of iron and 400 mcg of folic acid) or folic acid alone (400 mcg of folic acid) from enrolment until delivery.
Outcomes	1. Birthweight. 2. Duration of gestation. 3. Maternal Hb concentration.
Notes	Women's risk of spontaneous and recurrent miscarriage is unclear. Women's nutritional status is unclear. Sample size calculation: based on a 25% reduction in low birthweight between either iron-folic acid or multiple micronutrient and folic acid (control) groups. Compliance: the number of remaining capsules was reported by the village doctor who visited the women every 2 weeks. The level of compliance with the supplementation was high in all treatment groups. Location: Shaanxi Province, China. Timeframe: August 2002 to January 2006.

Risk of bias

Bias	Authors' judgement	Support for judgement

Zeng 2008 *(Continued)*

Random sequence generation (selection bias)	Low risk	"Randomisation of villages was stratified by county with a fixed ratio of treatments (1:1:1) and blocking of 15 ..... The randomisation schedule was generated off site with a pseudo-random number generator....." pg 2, pgh 3.
Allocation concealment (selection bias)	Low risk	"A treatment colour code was assigned to each village based on the treatment allocation schedule. The treatment codes were opened only once all data had been collected." pg 2, pgh 3.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"A treatment colour code was assigned to each village based on the treatment allocation schedule. The treatment codes were opened only once all data had been collected." pg 2, pgh 3.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No information provided about blinding of outcome assessors.
Incomplete outcome data (attrition bias) All outcomes	High risk	121/1666 missing in folic acid, 67/1537 missing in iron-folic acid, 88/1494 missing in multiple micronutrients in birthweight analysis. No reasons for missing data. Amount of missing data from other outcomes unknown. Fig 1; table 4.
Selective reporting (reporting bias)	Low risk	Study protocol is available and all primary outcomes were reported as described in the protocol.
Other bias	Unclear risk	From the 531 clusters, 13 clusters were excluded due to no birth outcomes in the excluded clusters. The number of clusters excluded was unbalanced across the intervention groups which may have been due to important baseline differences.

B-HCG: Beta human chorionic gonadotropin
BMI: body mass index
F: folic acid
Hb: haemoglobin
HbCC: haemoglobin C disease
HbSC:haemoglobin SC disease
HbSS: haemoglobin sickle cell disease
HELLP syndrome: haemolysis, elevated liver enzymes, low platelet count syndrome
HIV-1: Human Immunodeficiency Virus-1
HOFPP: Hungarian Optimal Family Planning Programme
IQR: interquartile range
IFA: iron and folic acid
IU: international units
IVF-ET: in vitro fertilization and embryo transfer
mcg: micrograms
mg/mL: milligrams per millilitre
MF: multivitamins with folic acid
mg: milligrams
MMN: multiple micronutrient
MRDR: modified relative dose-response
MV: multivitamins without folic acid
MRC: Medical Research Council
NTD: neural tube defect
P: progesterone
PAI-1: plasminogen activator inhibitor-1
PAI-2: plasminogen activator inhibitor-2
PCV: packed cell volume
sTfR: Soluble transferrin receptor
UK: United Kingdom

UNIMMAP: United Nations International Multiple Micronutrient Preparation
USA: United States of America
WBC: white blood cell

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Baumslag 1970	Onset of supplementation was > 20 weeks' gestation. Women were supplemented with either iron, iron and folic acid or iron, folic acid and vitamin B12 from "after the 24th week of pregnancy".
Biswas 1984	Unclear of the gestational age at which women entered the trial.
Blot 1981	Onset of supplementation was > 20 weeks' gestation. Supplementation with either iron and folic acid or iron alone occurred "at the end of the 6th month of pregnancy". Unclear if women were randomised to the treatment groups.
Chanarin 1968	Onset of supplementation was > 20 weeks' gestation. Women were given a folic acid supplement after the 20th week of pregnancy. Abortion was reported according to folic acid status at 15 weeks, prior to supplementation.
Chelchowska 2004	No relevant clinical outcomes, reports biochemical markers of antioxidant status only.
Christian 2003	Data for main outcomes of interest were not reported in a form that could be included in the analysis. Perinatal death was reported which included stillbirths (gestational age >= 28 weeks) and death among infants in the first 7 days of life. Miscarriage data (defined as fetal loss < 28 weeks' gestation age) was not provided.
Colman 1974	Onset of supplementation was > 20 weeks' gestation. Women were supplemented "during the final month of pregnancy". Outcomes reported included folic acid red cell and serum folic acid concentration and haemoglobin concentration.
Correia 1982	No main outcomes of interest reported. Outcomes presented in the study were fetal weight (birthweight) and placental weight. Women's risk of spontaneous and recurrent miscarriage is unclear.
Coutsoudis 1999	Onset of supplementation was > 20 weeks' gestation. Women were given vitamin A and beta-carotene "during the third trimester of pregnancy".
Dawson 1962	Onset of supplementation was > 20 weeks' gestation. Women were supplemented with folic acid "on or after the 28th week". Group allocation was not done randomly. Reported outcomes include incidence of folic acid deficiency and megaloblastic anaemia, and haemoglobin concentration.
Edelstein 1968	Onset of supplementation was > 20 weeks' gestation. Supplementation was started at the 28th week of pregnancy. Outcomes reported included serum folate activity and serum folate, urinary formiminoglutamic acid, serum vitamin B12, mean haemoglobin and haematocrit values.
Ferguson 1955	Only 24 (9%) of the 269 women in the trial began to participate before 15 weeks' gestation and outcomes not reported separately according to gestation at enrolment.
Feyi-Waboso 2005	Onset of supplementation was 20 or more weeks' gestation.
Fletcher 1971	No inclusion/exclusion criteria reported, unclear of gestational age at enrolment to the study, reports combined outcomes for "antepartum and threatened or complete abortion" and "stillbirth or neonatal death or congenital malformation" (not reported separately).
Giles 1971	Onset of supplementation was > 20 weeks' gestation for a large proportion of the participants.

Study	Reason for exclusion
	4 groups in the study, 2 of which involved supplementation after 20 weeks' gestation. Results were not reported separately between groups.
Hampel 1974	Unclear of the gestational age at which women entered the trial.
Hankin 1966	No main outcomes reported. Supplementation was from "approximately 20 weeks", no clinically relevant outcomes, outcomes relating to vitamin C status in plasma and breast milk reported.
Hekmatdoost 2011	The intervention assessed the effectiveness of different forms of the same vitamin - folate (folic acid vs 5-methylenetetrahydrofolate (MTHF)) against each other. There was no placebo or control group.
Hibbard 1969	No main outcomes reported. Biochemical measures of blood folate status reported.
Hunt 1984	All women received a multivitamin in addition to the zinc supplement or placebo.
Huybregts 2009	Both groups received a multivitamin supplement (same vitamin content in each group).
Kaestel 2005	Women were recruited until late pregnancy and onset of supplementation occurred after 20 weeks.
Laurence 1981	No main outcomes or pregnancy loss outcomes reported. Miscarriage reported in those women where there was a neural tube defect, but not in all women according to treatment group.
Lin 2010	Intervention assessed effect of nutritional supplement besides vitamins. No main outcomes reported.
Lira 1989	No main outcomes reported. Biochemical measures of iron and folate status reported.
Lumeng 1976	Unclear gestational age at enrolment, 5 women were excluded due to abortion, premature labour, inadequate dietary records or missing more than 3 prenatal visits. Exclusions were not reported by group allocation. Outcomes related to maternal and fetal plasma levels of pyridoxal 5'-phosphate and coenzyme saturation of aspartate aminotransferase and alanine aminotransferase in maternal erthrocytes were reported.
Marya 1981	Onset of supplementation was > 20 weeks' gestation. Women were supplemented with vitamin D "throughout the 3rd trimester".
Meirinho 1987	No clinical outcomes reported. Maternal plasma concentrations of trophoblastic protein SP1 were reported.
Metz 1965	Onset of supplementation was > 20 weeks' gestation. Women were supplemented with either iron or iron and folic acid, or iron, folic acid and vitamin B12. Supplementation was started after the 24th week of pregnancy.
Mock 2002	No main outcomes reported. Women were enrolled in either early or late pregnancy. Biochemical measures of biotin status reported.
Moldenhauer 2002	No main outcomes reported. Unclear if this is a cohort study or randomised trial. Women in this study were participating in a randomised placebo-controlled trial of calcium supplementation, and completed a dietary assessment at 12-21 weeks' gestation and 29-31 weeks' gestation. Unclear whether all women took a standard prenatal multivitamin or just women in the placebo group. Results are presented according to "teens", "twins" and "singleton" pregnancies, not according to whether women took the sup-

Study	Reason for exclusion
	plement or not. Outcomes reported included dietary intakes of vitamin C and E (with and without the contribution of the prenatal vitamin supplement).
Owen 1966	Onset of supplementation was > 20 weeks' gestation. Women supplemented with oral vitamin K1 "several days before delivery".
Potdar 2014	Study was a food intervention trial.
Ross 1985	Unclear about content of vitamin supplements. Women were supplemented with high or low 'bulk' dietary supplements with vitamins added; however, the vitamin supplements added were not specified.
Schuster 1984	Unclear of gestation at enrolment to the trial. No pregnancy loss outcomes reported.
Semba 2001	No main outcomes reported. Women enrolled between 18 and 28 weeks' gestation, no clinical outcomes reported, only haemoglobin and plasma erythropoietin concentrations.
Shu 2002	Both groups received a multivitamin (same vitamin content in both groups).
Smithells 1981	Non-randomised study of periconceptional multivitamin supplementation for the prevention of neural tube defects.
Suharno 1993	No main outcomes reported. Anaemic pregnant women were enrolled between 16 and 24 weeks' gestation. The only clinical outcome reported was the percentage of women with anaemia following treatment with a combination of vitamin A and iron or placebo.
Tanumihardjo 2002	No main outcomes reported. Mean gestation at enrolment was 17.6 weeks, no clinical outcomes reported, markers of vitamin A and iron status reported.
Taylor 1982	No main outcomes reported. Haematological features and serum ferritin were determined. No reports on pregnancy loss.
Thauvin 1992	No main outcomes reported. Women were supplemented from 3 months' gestation, data on pregnancy outcomes including spontaneous abortion were collected but not reported.
Trigg 1976	Unclear of gestation at enrolment to the trial.
Ulrich 1999	Non-randomised study. Observational cohort study of folic acid users, randomised to different doses of folic acid, but no controls.
Villamor 2002	No main outcomes reported. Women enrolled between 12 and 27 weeks' gestation, no pregnancy loss or main outcomes reported, only reports measures of weight gain during pregnancy.
Vutyavanich 1995	No main outcomes reported. Women were enrolled in the study if they were less than 17 weeks' gestation; however, no pregnancy loss or main outcomes were reported, only measures of nausea and vomiting.
Wehby 2012	This trial involved only one vitamin compared at different doses.
Young 2015	No relevant outcomes were reported in this study.

Characteristics of studies awaiting assessment *[ordered by study ID]*

Adu-Afarwuah 2015

Methods	Partially double-blind, individually-randomised controlled trial.
Participants	1320 pregnant women around 20 gestational weeks.
Interventions	Women received 1 of 3 supplements daily until delivery: 60 mg Fe + 400 µg folic acid (IFA), or 1-2 recommended dietary allowances of 18 micronutrients including 20 mg Fe (MMN), or SQ-LNS with the same nutrient levels as in MMN, plus 4 additional minerals as well as macronutrients contributing 118 kcal (LNS).
Outcomes	Haemoglobin concentration (g/L) and 2 markers of iron status, zinc protoporphyrin (ZPP, µmol/mol heme) and transferrin receptor (TfR, mg/L) were assessed.
Notes	Only study abstract available and the composition of the supplement is not clear. Need to see full text.

Agarwal 2012a

Methods	Individually-randomised controlled trial.
Participants	50 women of recurrent of abortions (more than 2).
Interventions	Women received Vitamin B12 1500 mcg, Vitamin B6 10 mg and folic acid 5 mg daily throughout pregnancy.
Outcomes	1. Abortion. 2. Pre-eclampsia. 3. IUGR. 4. Preterm labour.
Notes	Only study abstract available, comparison group also received same intervention but duration is different.

Frenzel 1956

Methods	Unclear.
Participants	Unclear.
Interventions	Unclear.
Outcomes	Unclear.
Notes	A copy of the paper could not be located.

Prado 2015

Methods	Randomised cohorts.
Participants	Pregnant women and infants.
Interventions	Various formulations of lipid-based nutrient supplements (LNS) during pregnancy and infancy or infancy alone.
Outcomes	1. Association between linear growth and language development 2. Association between 18-month language scores and 3. 18-month length-for-age z-score (LAZ) 4. LAZ at age 6 or 9 months and 5. The change in LAZ between infancy (6 or 9 months) and 18 months
Notes	Abstract only, no specification what LNS is in abstract.

IFA: iron and folic acid
IUGR: Intrauterine growth restriction
MMN: multiple micronutrient

Characteristics of ongoing studies *[ordered by study ID]*

Johns 2004

Trial name or title	The effect of antioxidant supplementation on women with threatened miscarriage.
Methods	Randomised controlled trial.
Participants	580 women who present with first trimester bleeding.
Interventions	Vitamin C 1000 mg and Vitamin E 400 IU versus placebo.
Outcomes	1. Incidence of miscarriage. 2. Late miscarriage. 3. Preterm labour. 4. Preterm pre-labour rupture of the membranes. 5. Fetal growth restriction. 6. Pre-eclampsia.
Starting date	01/03/2004.
Contact information	**Dr Jemma Johns** UCLH/UCL Research & Development Governance Committee Research and Development Directorate University College London Hospitals NHS Trust 1st Floor, Maple House 149 Tottenham Court Road
Notes	Listed as completed.

IU: internation unit(s)

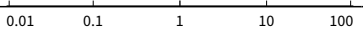
DATA AND ANALYSES

Comparison 1. Vitamin C plus vitamin E versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Total fetal loss	7	18949	Risk Ratio (M-H, Fixed, 95% CI)	1.14 [0.92, 1.40]
2 Early or late miscarriage	4	13346	Risk Ratio (M-H, Fixed, 95% CI)	0.90 [0.65, 1.26]
3 Stillbirth	7	21442	Risk Ratio (M-H, Fixed, 95% CI)	1.31 [0.97, 1.76]
4 Congenital malformations	5	8334	Risk Ratio (M-H, Fixed, 95% CI)	1.17 [0.84, 1.62]
5 Any adverse effects of vitamin supplementation sufficient to stop supplementation	1	739	Risk Ratio (M-H, Fixed, 95% CI)	1.16 [0.39, 3.41]

Analysis 1.1. Comparison 1 Vitamin C plus vitamin E versus placebo, Outcome 1 Total fetal loss.

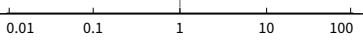
Study or subgroup	Vitamin C & E n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Chappell 1999	1/141	2/142		1.22%	0.5[0.05,5.49]
McCance 2010	14/379	12/382		7.29%	1.18[0.55,2.51]
Poston 2006	35/1393	19/1391		11.6%	1.84[1.06,3.2]
Roberts 2010	93/4993	95/4976		58.05%	0.98[0.73,1.29]
Rumbold 2006	11/935	13/942		7.9%	0.85[0.38,1.89]
Spinnato 2007	11/371	13/368		7.96%	0.84[0.38,1.85]
Xu 2010	21/1243	10/1293		5.98%	2.18[1.03,4.62]
Total (95% CI)	**9455**	**9494**		**100%**	**1.14[0.92,1.4]**
Total events: 186 (Vitamin C & E), 164 (Control)					
Heterogeneity: Tau^2=0; Chi^2=8.46, df=6(P=0.21); I^2=29.12%					
Test for overall effect: Z=1.21(P=0.23)					



Favours [vitamin C & E] Favours [no vitamin C]

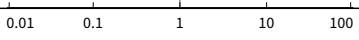
Analysis 1.2. Comparison 1 Vitamin C plus vitamin E versus placebo, Outcome 2 Early or late miscarriage.

Study or subgroup	Vitamin C & E n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
McCance 2010	4/379	4/382		5.45%	1.01[0.25,4]
Roberts 2010	55/4993	59/4976		80.88%	0.93[0.64,1.34]
Rumbold 2006	3/935	7/942		9.54%	0.43[0.11,1.66]
Spinnato 2007	4/371	3/368		4.12%	1.32[0.3,5.87]
Total (95% CI)	**6678**	**6668**		**100%**	**0.9[0.65,1.26]**
Total events: 66 (Vitamin C & E), 73 (Control)					



Favours [vitamin C&E] Favours [no vitamin C]

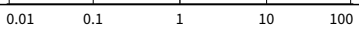
Study or subgroup	Vitamin C & E n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Heterogeneity: Tau²=0; Chi²=1.45, df=3(P=0.69); I²=0%					
Test for overall effect: Z=0.61(P=0.54)					



Favours [vitamin C&E] Favours [no vitamin C]

Analysis 1.3. Comparison 1 Vitamin C plus vitamin E versus placebo, Outcome 3 Stillbirth.

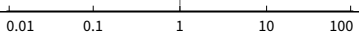
Study or subgroup	Vitamin C & E n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Chappell 1999	1/141	2/142		2.63%	0.5[0.05,5.49]
McCance 2010	10/379	8/382		10.5%	1.26[0.5,3.16]
Poston 2006	19/1369	7/1372		9.21%	2.72[1.15,6.45]
Roberts 2010	38/4993	36/4976		47.51%	1.05[0.67,1.66]
Rumbold 2006	8/935	6/942		7.88%	1.34[0.47,3.86]
Spinnato 2007	7/371	10/368		13.23%	0.69[0.27,1.8]
Xu 2010	10/1243	6/1293		7.75%	1.73[0.63,4.76]
Xu 2010	6/1243	1/1293		1.29%	6.24[0.75,51.77]
Total (95% CI)	**10674**	**10768**		**100%**	**1.31[0.97,1.76]**
Total events: 99 (Vitamin C & E), 76 (Control)					
Heterogeneity: Tau²=0; Chi²=8.35, df=7(P=0.3); I²=16.22%					
Test for overall effect: Z=1.77(P=0.08)					



Favours [vitamin C & E] Favours [no vitamin C]

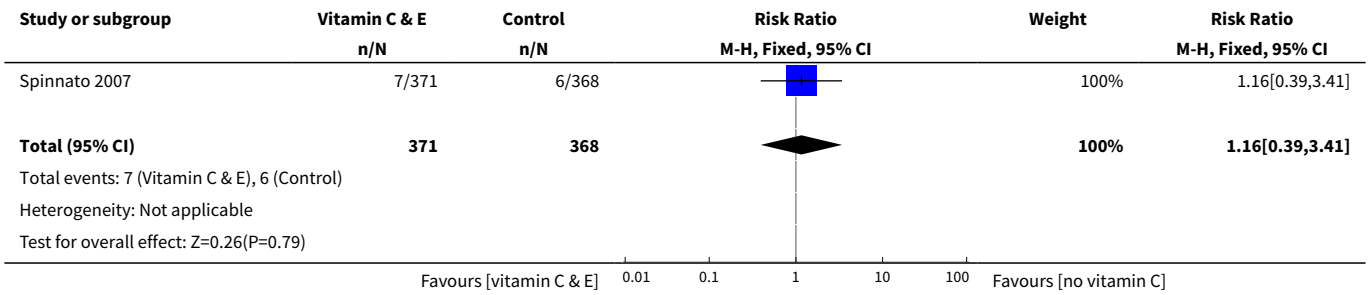
Analysis 1.4. Comparison 1 Vitamin C plus vitamin E versus placebo, Outcome 4 Congenital malformations.

Study or subgroup	Vitamin C & E n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
McCance 2010	12/378	17/382		26.32%	0.71[0.35,1.47]
Poston 2006	5/1393	4/1391		6.23%	1.25[0.34,4.64]
Spinnato 2007	1/371	2/368		3.13%	0.5[0.05,5.45]
Villar 2009	19/753	12/762		18.56%	1.6[0.78,3.28]
Xu 2010	37/1243	30/1293		45.77%	1.28[0.8,2.06]
Total (95% CI)	**4138**	**4196**		**100%**	**1.17[0.84,1.62]**
Total events: 74 (Vitamin C & E), 65 (Control)					
Heterogeneity: Tau²=0; Chi²=3.18, df=4(P=0.53); I²=0%					
Test for overall effect: Z=0.91(P=0.36)					



Favours [vitamin C & E] Favours [no vitamin C]

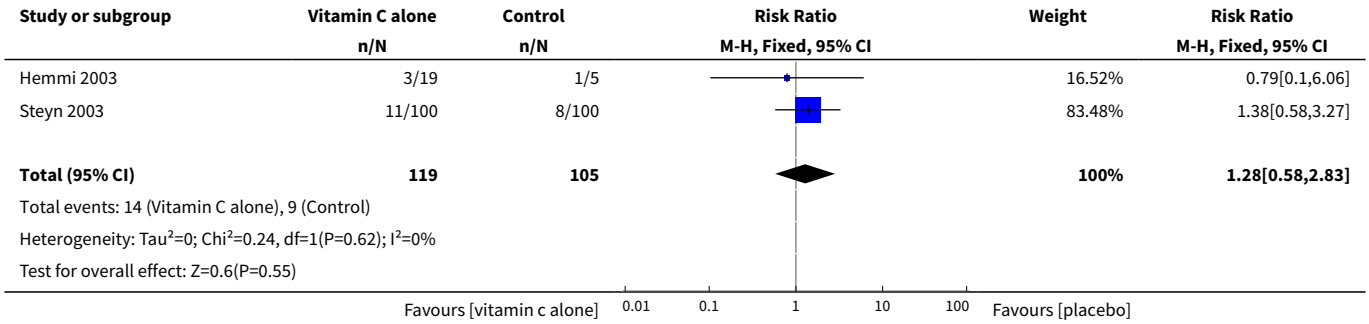
Analysis 1.5. Comparison 1 Vitamin C plus vitamin E versus placebo, Outcome 5 Any adverse effects of vitamin supplementation sufficient to stop supplementation.



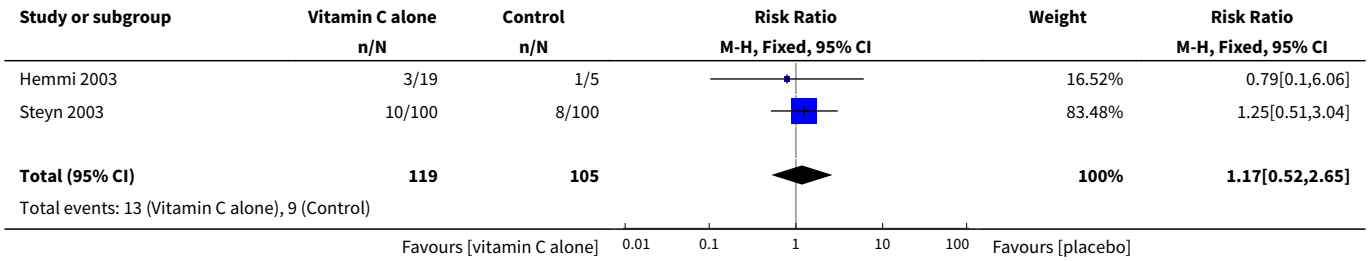
Comparison 2. Vitamin C versus no supplement/placebo

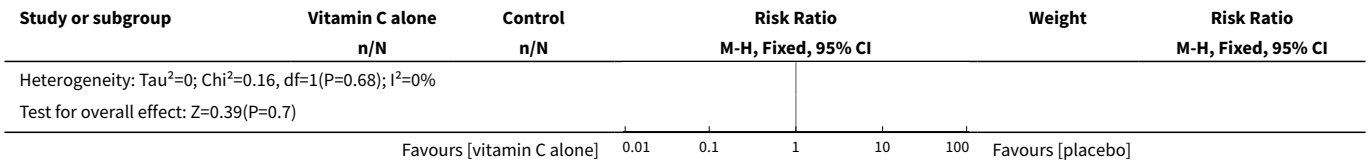
Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
1 Total fetal loss	2	224	Risk Ratio (M-H, Fixed, 95% CI)	1.28 [0.58, 2.83]
2 Early or late miscarriage	2	224	Risk Ratio (M-H, Fixed, 95% CI)	1.17 [0.52, 2.65]
3 Stillbirth	1	200	Risk Ratio (M-H, Fixed, 95% CI)	3.0 [0.12, 72.77]

Analysis 2.1. Comparison 2 Vitamin C versus no supplement/placebo, Outcome 1 Total fetal loss.

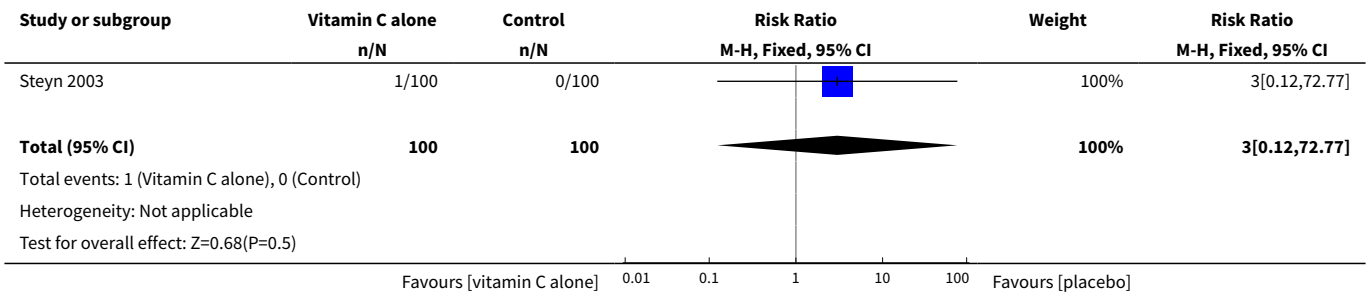


Analysis 2.2. Comparison 2 Vitamin C versus no supplement/placebo, Outcome 2 Early or late miscarriage.





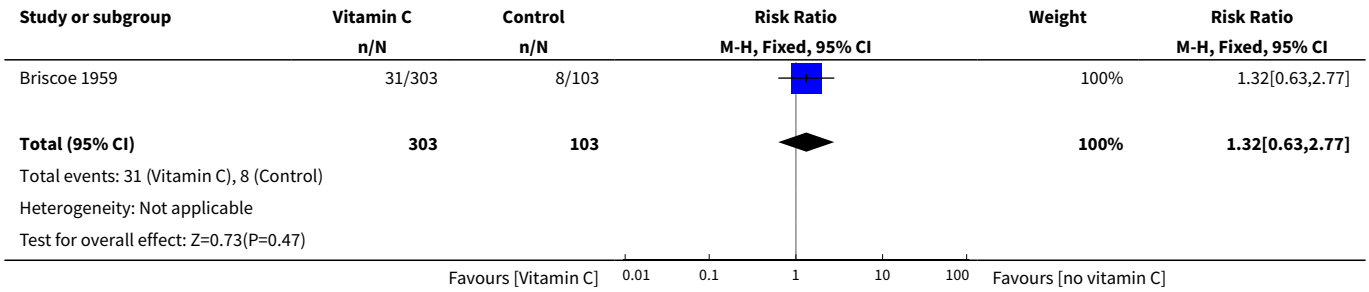
Analysis 2.3. Comparison 2 Vitamin C versus no supplement/placebo, Outcome 3 Stillbirth.



Comparison 3. Vitamin C plus multivitamins versus placebo plus multivitamins or multivitamins alone

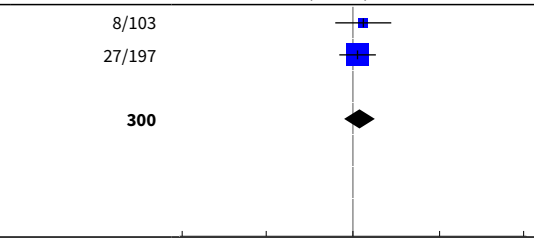
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Total fetal loss	1	406	Risk Ratio (M-H, Fixed, 95% CI)	1.32 [0.63, 2.77]
2 Early or late miscarriage	2	790	Risk Ratio (M-H, Fixed, 95% CI)	1.19 [0.79, 1.79]

Analysis 3.1. Comparison 3 Vitamin C plus multivitamins versus placebo plus multivitamins or multivitamins alone, Outcome 1 Total fetal loss.



Analysis 3.2. Comparison 3 Vitamin C plus multivitamins versus placebo plus multivitamins or multivitamins alone, Outcome 2 Early or late miscarriage.

Study or subgroup	Vitamin C n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Briscoe 1959	31/303	8/103		31.23%	1.32[0.63,2.77]
Hans 2010	29/187	27/197		68.77%	1.13[0.7,1.84]
Total (95% CI)	**490**	**300**		**100%**	**1.19[0.79,1.79]**
Total events: 60 (Vitamin C), 35 (Control)					
Heterogeneity: Tau^2=0; Chi^2=0.11, df=1(P=0.74); I^2=0%					
Test for overall effect: Z=0.84(P=0.4)					

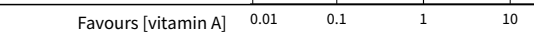


Comparison 4. Vitamin A plus iron and folate versus iron and folate

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Total fetal loss	3	1640	Risk Ratio (Fixed, 95% CI)	1.01 [0.61, 1.66]
2 Early or late miscarriage	2	1397	Risk Ratio (Fixed, 95% CI)	0.86 [0.46, 1.62]
3 Stillbirth	3	1640	Risk Ratio (Fixed, 95% CI)	1.29 [0.57, 2.91]

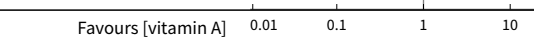
Analysis 4.1. Comparison 4 Vitamin A plus iron and folate versus iron and folate, Outcome 1 Total fetal loss.

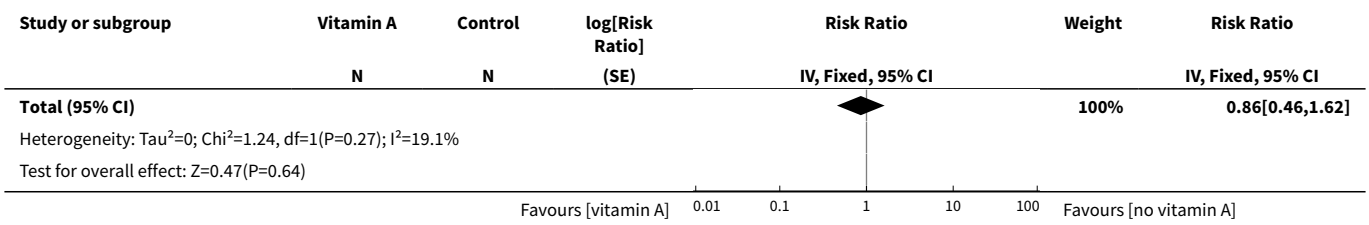
Study or subgroup	Vitamin A N	Control N	log[Risk Ratio] (SE)	Risk Ratio IV, Fixed, 95% CI	Weight	Risk Ratio IV, Fixed, 95% CI
Kumwenda 2002	340	357	0.4 (0.388)		42.63%	1.43[0.67,3.06]
Schmidt 2001	122	121	-0 (0.812)		9.75%	0.99[0.2,4.86]
Van den Broek 2006	468	232	-0.3 (0.367)		47.62%	0.74[0.36,1.52]
Total (95% CI)					**100%**	**1.01[0.61,1.66]**
Heterogeneity: Tau^2=0; Chi^2=1.52, df=2(P=0.47); I^2=0%						
Test for overall effect: Z=0.03(P=0.97)						



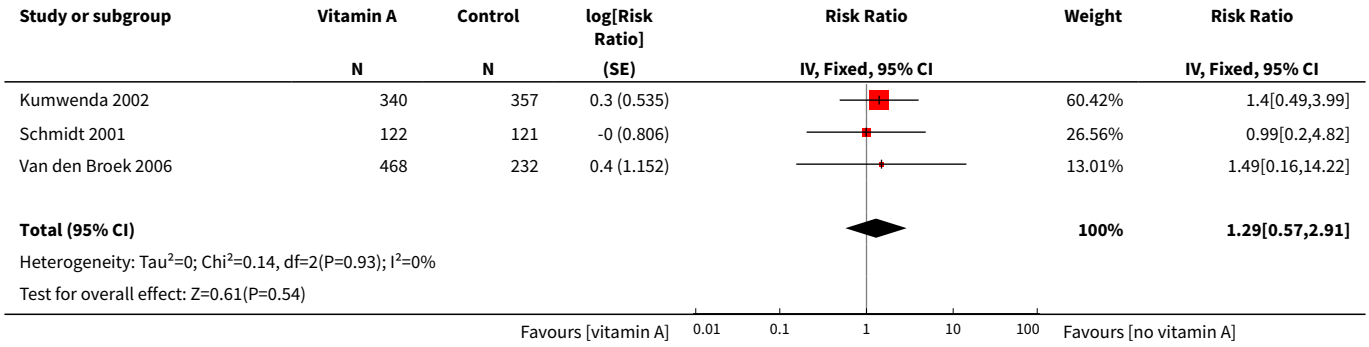
Analysis 4.2. Comparison 4 Vitamin A plus iron and folate versus iron and folate, Outcome 2 Early or late miscarriage.

Study or subgroup	Vitamin A N	Control N	log[Risk Ratio] (SE)	Risk Ratio IV, Fixed, 95% CI	Weight	Risk Ratio IV, Fixed, 95% CI
Kumwenda 2002	340	357	0.4 (0.581)		30.96%	1.47[0.47,4.59]
Van den Broek 2006	468	232	-0.4 (0.389)		69.04%	0.68[0.32,1.45]





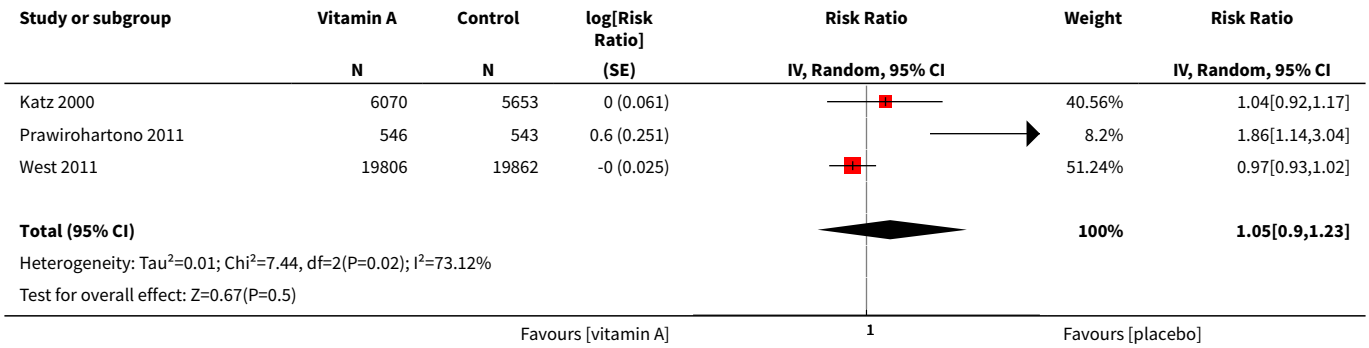
Analysis 4.3. Comparison 4 Vitamin A plus iron and folate versus iron and folate, Outcome 3 Stillbirth.



Comparison 5. Vitamin A versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Total fetal loss	3	52480	Risk Ratio (Random, 95% CI)	1.05 [0.90, 1.23]
2 Early of late miscarriage	1	39668	Risk Ratio (Fixed, 95% CI)	0.98 [0.92, 1.04]
3 Stillbirth	1	39668	Risk Ratio (Fixed, 95% CI)	0.95 [0.86, 1.06]

Analysis 5.1. Comparison 5 Vitamin A versus placebo, Outcome 1 Total fetal loss.



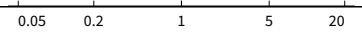
Analysis 5.2. Comparison 5 Vitamin A versus placebo, Outcome 2 Early of late miscarriage.

Study or subgroup	Vitamin A N	Control N	log[Risk Ratio] (SE)	Risk Ratio IV, Fixed, 95% CI	Weight	Risk Ratio IV, Fixed, 95% CI
West 2011	19806	19862	-0 (0.029)		100%	0.98[0.92,1.04]
Total (95% CI)					**100%**	**0.98[0.92,1.04]**
Heterogeneity: Not applicable						
Test for overall effect: Z=0.72(P=0.47)						

Favours [vitamin A] Favours [placebo]

Analysis 5.3. Comparison 5 Vitamin A versus placebo, Outcome 3 Stillbirth.

Study or subgroup	Vitamin A N	Control N	log[Risk Ratio] (SE)	Risk Ratio IV, Fixed, 95% CI	Weight	Risk Ratio IV, Fixed, 95% CI
West 2011	19806	19862	-0 (0.054)		100%	0.95[0.86,1.06]
Total (95% CI)					**100%**	**0.95[0.86,1.06]**
Heterogeneity: Not applicable						
Test for overall effect: Z=0.9(P=0.37)						



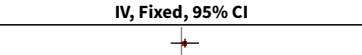
Favours [vitamin A] Favours [placebo]

Comparison 6. Beta-carotene versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Total fetal loss	2	51163	Risk Ratio (Fixed, 95% CI)	1.02 [0.98, 1.07]
2 Early or late miscarriage	1	39860	Risk Ratio (Fixed, 95% CI)	1.00 [0.94, 1.06]
3 Stillbirth	1	39860	Risk Ratio (Fixed, 95% CI)	1.09 [0.98, 1.20]

Analysis 6.1. Comparison 6 Beta-carotene versus placebo, Outcome 1 Total fetal loss.

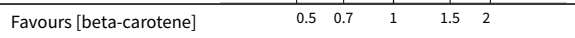
Study or subgroup	Beta-carotene N	Control N	log[Risk Ratio] (SE)	Risk Ratio IV, Fixed, 95% CI	Weight	Risk Ratio IV, Fixed, 95% CI
Katz 2000	5650	5653	0 (0.061)		13.97%	1.03[0.91,1.16]
West 2011	19998	19862	0 (0.025)		86.03%	1.02[0.97,1.07]
Total (95% CI)					**100%**	**1.02[0.98,1.07]**
Heterogeneity: $Tau^2=0$; $Chi^2=0.02$, df=1(P=0.89); $I^2=0\%$						
Test for overall effect: Z=0.94(P=0.35)						



Favours [beta-carotene] Favours [placebo]

Analysis 6.2. Comparison 6 Beta-carotene versus placebo, Outcome 2 Early or late miscarriage.

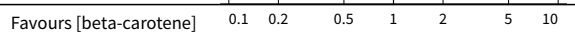
Study or subgroup	Beta-carotene N	Control N	log[Risk Ratio] (SE)	Risk Ratio IV, Fixed, 95% CI	Weight	Risk Ratio IV, Fixed, 95% CI
West 2011	19998	19862	-0 (0.029)		100%	1[0.94,1.06]
Total (95% CI)					**100%**	**1[0.94,1.06]**
Heterogeneity: Not applicable						
Test for overall effect: Z=0.07(P=0.94)						



Favours [beta-carotene] Favours [placebo]

Analysis 6.3. Comparison 6 Beta-carotene versus placebo, Outcome 3 Stillbirth.

Study or subgroup	Beta-carotene N	Control N	log[Risk Ratio] (SE)	Risk Ratio IV, Fixed, 95% CI	Weight	Risk Ratio IV, Fixed, 95% CI
West 2011	19998	19862	0.1 (0.052)		100%	1.09[0.98,1.2]
Total (95% CI)					**100%**	**1.09[0.98,1.2]**
Heterogeneity: Not applicable						
Test for overall effect: Z=1.62(P=0.1)						



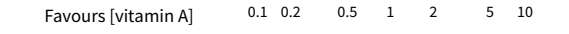
Favours [beta-carotene] Favours [placebo]

Comparison 7. Vitamin A or beta-carotene versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Total fetal loss	1	17373	Risk Ratio (Fixed, 95% CI)	1.05 [0.91, 1.21]

Analysis 7.1. Comparison 7 Vitamin A or beta-carotene versus placebo, Outcome 1 Total fetal loss.

Study or subgroup	Vitamin A N	Control N	log[Risk Ratio] (SE)	Risk Ratio IV, Fixed, 95% CI	Weight	Risk Ratio IV, Fixed, 95% CI
Katz 2000	11720	5653	0 (0.071)		100%	1.05[0.91,1.21]
Total (95% CI)					**100%**	**1.05[0.91,1.21]**
Heterogeneity: Not applicable						
Test for overall effect: Z=0.69(P=0.49)						



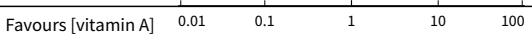
Favours [vitamin A] Favours [placebo]

Comparison 8. Vitamin A (with/without multivitamins) versus multivitamins or placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Total fetal loss	1	1074	Risk Ratio (Fixed, 95% CI)	0.80 [0.53, 1.21]
2 Early or late miscarriage	1	1075	Risk Ratio (Fixed, 95% CI)	0.76 [0.37, 1.55]
3 Stillbirth	1	1075	Risk Ratio (Fixed, 95% CI)	1.04 [0.60, 1.79]

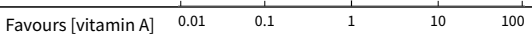
Analysis 8.1. Comparison 8 Vitamin A (with/without multivitamins) versus multivitamins or placebo, Outcome 1 Total fetal loss.

Study or subgroup	Vitamin A N	Control N	log[Risk Ratio] (SE)	Risk Ratio IV, Fixed, 95% CI	Weight	Risk Ratio IV, Fixed, 95% CI
Fawzi 1998	538	536	-0.2 (0.211)		100%	0.8[0.53,1.21]
Total (95% CI)					**100%**	**0.8[0.53,1.21]**
Heterogeneity: Not applicable						
Test for overall effect: Z=1.06(P=0.29)						



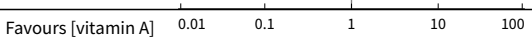
Analysis 8.2. Comparison 8 Vitamin A (with/without multivitamins) versus multivitamins or placebo, Outcome 2 Early or late miscarriage.

Study or subgroup	Vitamin A N	Control N	log[Risk Ratio] (SE)	Risk Ratio IV, Fixed, 95% CI	Weight	Risk Ratio IV, Fixed, 95% CI
Fawzi 1998	539	536	-0.3 (0.363)		100%	0.76[0.37,1.55]
Total (95% CI)					**100%**	**0.76[0.37,1.55]**
Heterogeneity: Tau²=0; Chi²=0, df=0(P<0.0001); I²=100%						
Test for overall effect: Z=0.75(P=0.45)						



Analysis 8.3. Comparison 8 Vitamin A (with/without multivitamins) versus multivitamins or placebo, Outcome 3 Stillbirth.

Study or subgroup	Vitamin A N	Control N	log[Risk Ratio] (SE)	Risk Ratio IV, Fixed, 95% CI	Weight	Risk Ratio IV, Fixed, 95% CI
Fawzi 1998	539	536	0 (0.279)		100%	1.04[0.6,1.79]
Total (95% CI)					**100%**	**1.04[0.6,1.79]**
Heterogeneity: Not applicable						
Test for overall effect: Z=0.13(P=0.9)						

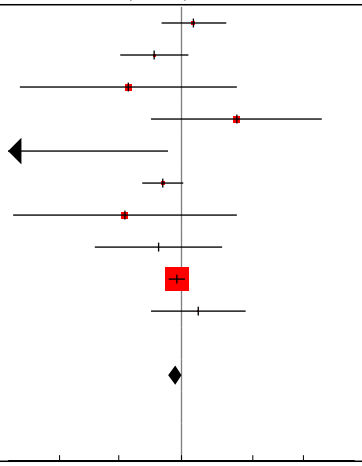


Comparison 9. Multivitamin plus iron and folic acid versus iron and folic acid

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Total fetal loss	10	94948	Risk Ratio (Fixed, 95% CI)	0.96 [0.93, 1.00]
2 Early or late miscarriage	10	94948	Risk Ratio (Fixed, 95% CI)	0.98 [0.94, 1.03]
3 Stillbirth	10	79851	Risk Ratio (Fixed, 95% CI)	0.92 [0.85, 0.99]
4 Congenital malformation	1	1200	Risk Ratio (M-H, Fixed, 95% CI)	1.0 [0.14, 7.08]

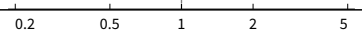
Analysis 9.1. Comparison 9 Multivitamin plus iron and folic acid versus iron and folic acid, Outcome 1 Total fetal loss.

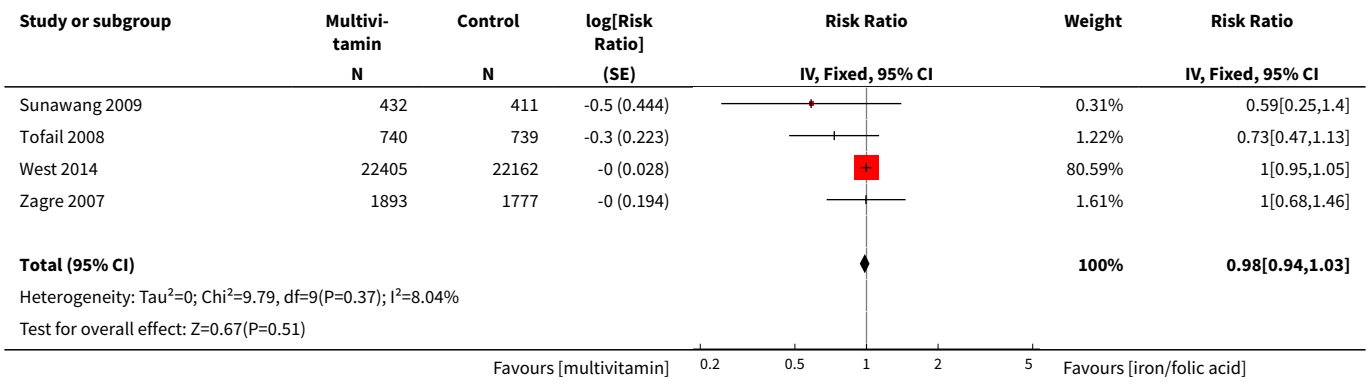
Study or subgroup	Multivitamin N	Control N	log[Risk Ratio] (SE)	Risk Ratio IV, Fixed, 95% CI	Weight	Risk Ratio IV, Fixed, 95% CI
Bhutta 2009	947	1038	0.1 (0.094)		4.78%	1.07[0.89,1.29]
Fawzi 2007	4214	4214	-0.2 (0.098)		4.36%	0.86[0.71,1.04]
Osrin 2005	600	600	-0.3 (0.315)		0.42%	0.74[0.4,1.37]
Roberfroid 2008	714	712	0.3 (0.248)		0.68%	1.37[0.84,2.22]
Rumiris 2006	29	31	-2.9 (1.43)		0.02%	0.06[0,0.93]
Summit 2008	15804	15486	-0.1 (0.059)		12.02%	0.9[0.8,1.01]
Sunawang 2009	432	411	-0.3 (0.325)		0.4%	0.72[0.38,1.37]
Tofail 2008	740	739	-0.1 (0.185)		1.22%	0.88[0.61,1.26]
West 2014	22405	22162	-0 (0.024)		73.85%	0.97[0.93,1.02]
Zagre 2007	1893	1777	0.1 (0.137)		2.25%	1.1[0.84,1.44]
Total (95% CI)					**100%**	**0.96[0.93,1]**
Heterogeneity: Tau²=0; Chi²=13, df=9(P=0.16); I²=30.75%						
Test for overall effect: Z=1.76(P=0.08)						



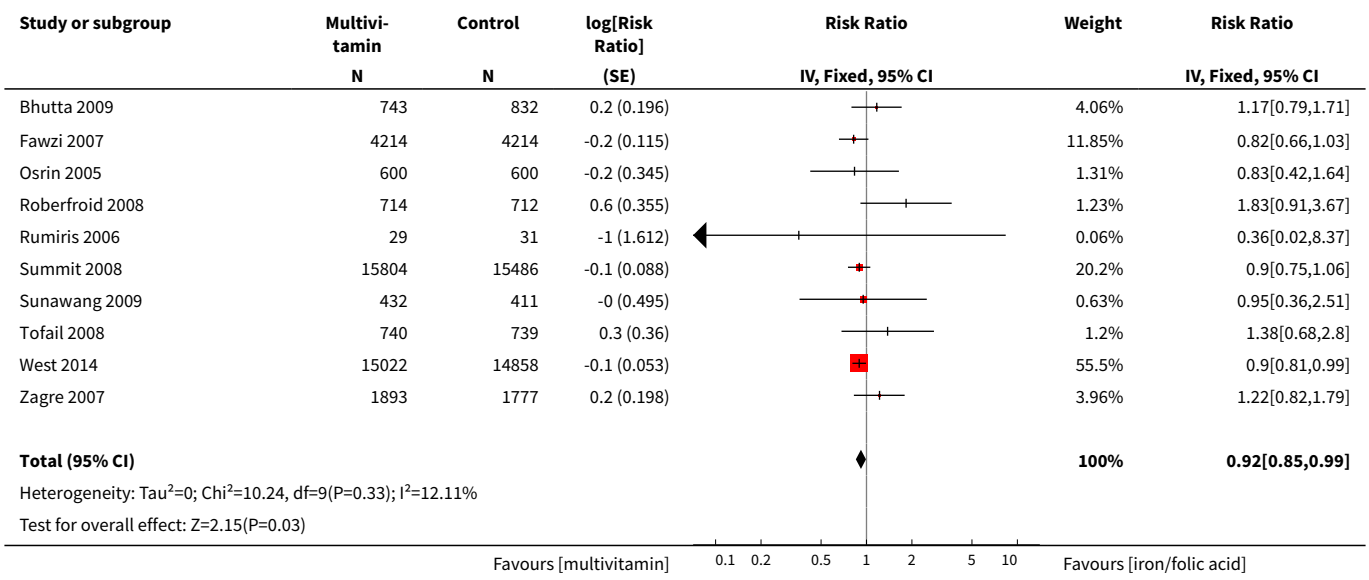
Analysis 9.2. Comparison 9 Multivitamin plus iron and folic acid versus iron and folic acid, Outcome 2 Early or late miscarriage.

Study or subgroup	Multivitamin N	Control N	log[Risk Ratio] (SE)	Risk Ratio IV, Fixed, 95% CI	Weight	Risk Ratio IV, Fixed, 95% CI
Bhutta 2009	947	1038	0 (0.112)		4.84%	1.05[0.84,1.31]
Fawzi 2007	4214	4214	-0 (0.197)		1.57%	0.96[0.65,1.41]
Osrin 2005	600	600	-0.9 (0.835)		0.09%	0.4[0.08,2.05]
Roberfroid 2008	714	712	-0 (0.361)		0.47%	1[0.49,2.02]
Rumiris 2006	29	31	-2.8 (1.43)		0.03%	0.06[0,1.03]
Summit 2008	15804	15486	-0.1 (0.081)		9.27%	0.9[0.77,1.06]

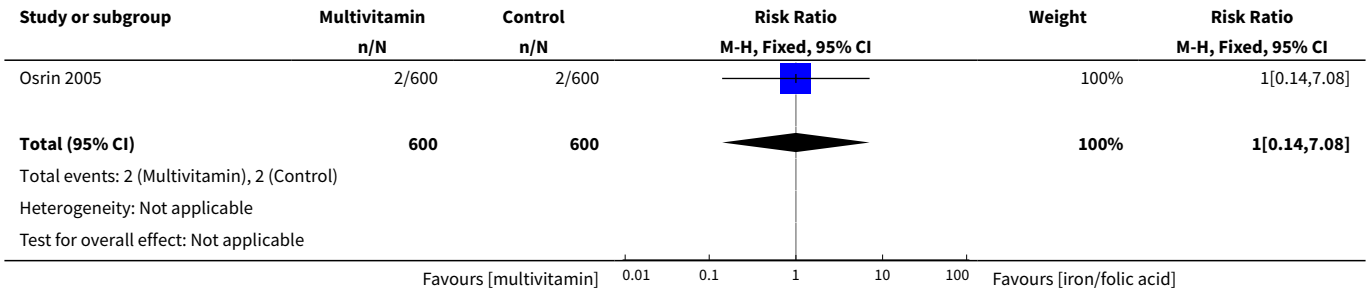




Analysis 9.3. Comparison 9 Multivitamin plus iron and folic acid versus iron and folic acid, Outcome 3 Stillbirth.



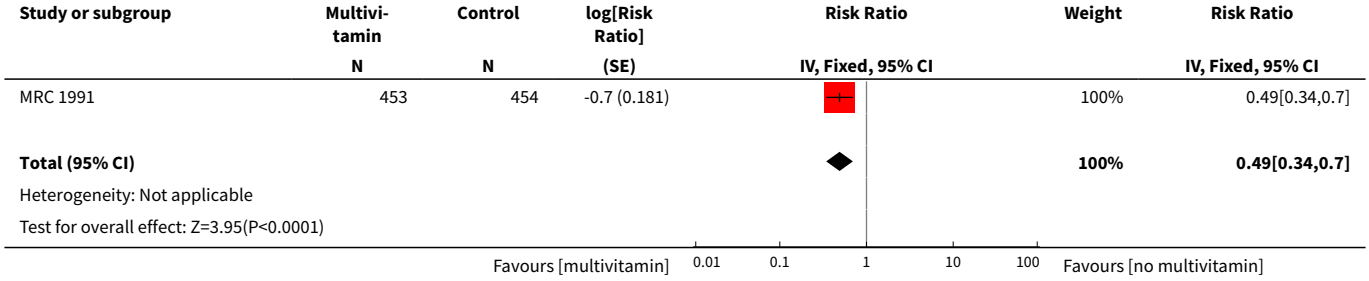
Analysis 9.4. Comparison 9 Multivitamin plus iron and folic acid versus iron and folic acid, Outcome 4 Congenital malformation.



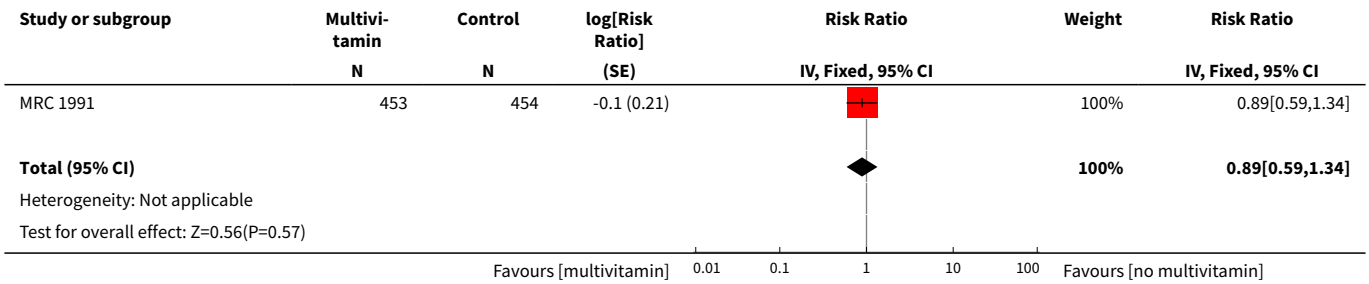
Comparison 10. Multivitamin without folic acid versus no multivitamin/folic acid

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Total fetal loss	1	907	Risk Ratio (Fixed, 95% CI)	0.49 [0.34, 0.70]
2 Early or late miscarriage	1	907	Risk Ratio (Fixed, 95% CI)	0.89 [0.59, 1.34]
3 Stillbirth	1	907	Risk Ratio (Fixed, 95% CI)	0.14 [0.01, 2.77]
4 Congenital malformations	1	907	Risk Ratio (M-H, Fixed, 95% CI)	1.60 [0.53, 4.86]

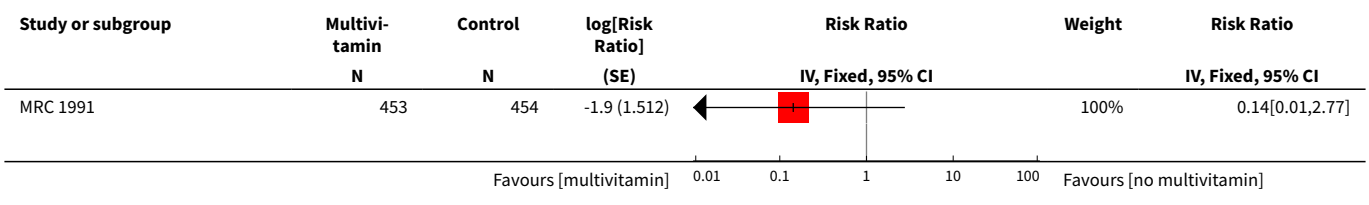
Analysis 10.1. Comparison 10 Multivitamin without folic acid versus no multivitamin/folic acid, Outcome 1 Total fetal loss.

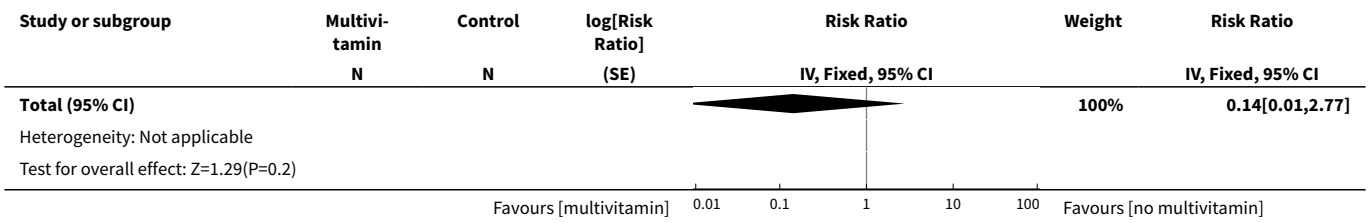


Analysis 10.2. Comparison 10 Multivitamin without folic acid versus no multivitamin/folic acid, Outcome 2 Early or late miscarriage.

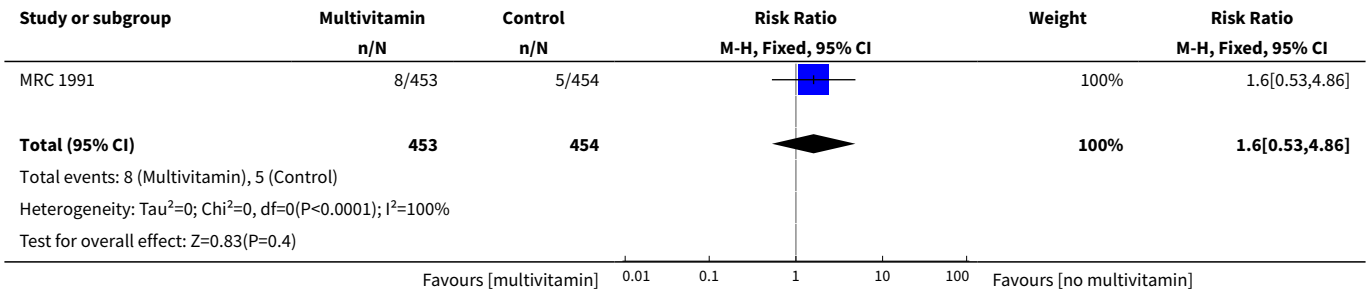


Analysis 10.3. Comparison 10 Multivitamin without folic acid versus no multivitamin/folic acid, Outcome 3 Stillbirth.





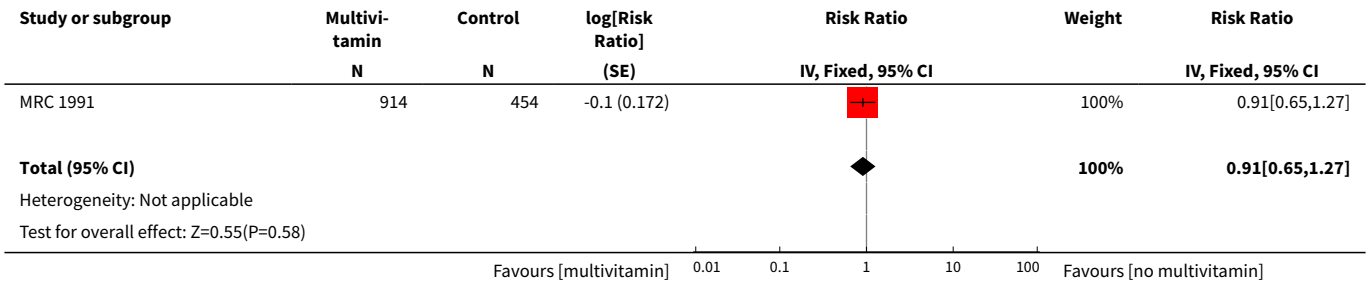
Analysis 10.4. Comparison 10 Multivitamin without folic acid versus no multivitamin/folic acid, Outcome 4 Congenital malformations.



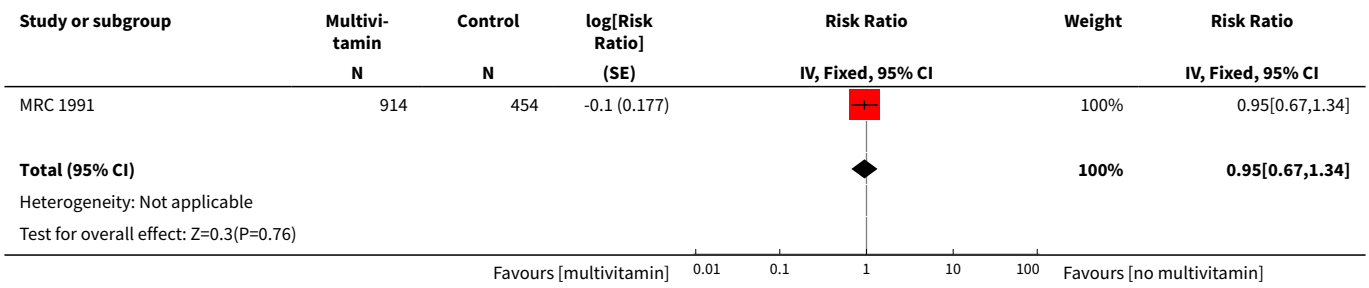
Comparison 11. Multivitamin with/without folic acid versus no multivitamin/folic acid

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
1 Total fetal loss	1	1368	Risk Ratio (Fixed, 95% CI)	0.91 [0.65, 1.27]
2 Early or late miscarriage	1	1368	Risk Ratio (Fixed, 95% CI)	0.95 [0.67, 1.34]
3 Stillbirth	1	1368	Risk Ratio (Fixed, 95% CI)	0.33 [0.06, 1.98]
4 Congenital malformations	1	1368	Risk Ratio (M-H, Fixed, 95% CI)	1.99 [0.75, 5.26]

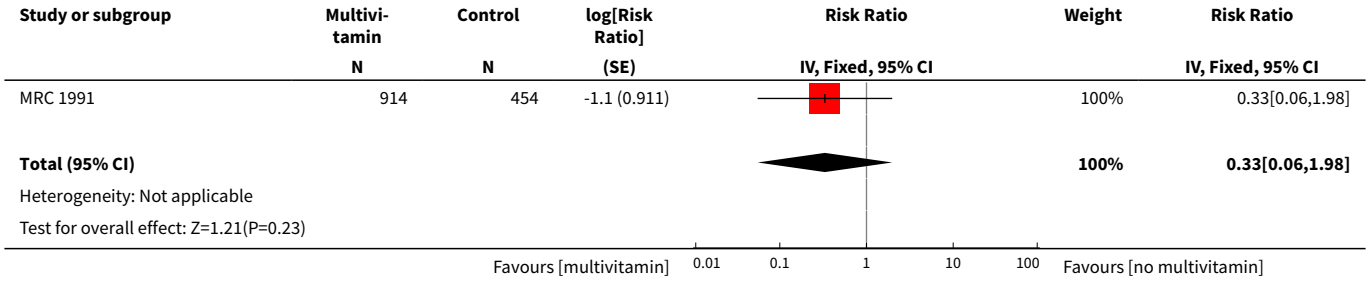
Analysis 11.1. Comparison 11 Multivitamin with/without folic acid versus no multivitamin/folic acid, Outcome 1 Total fetal loss.



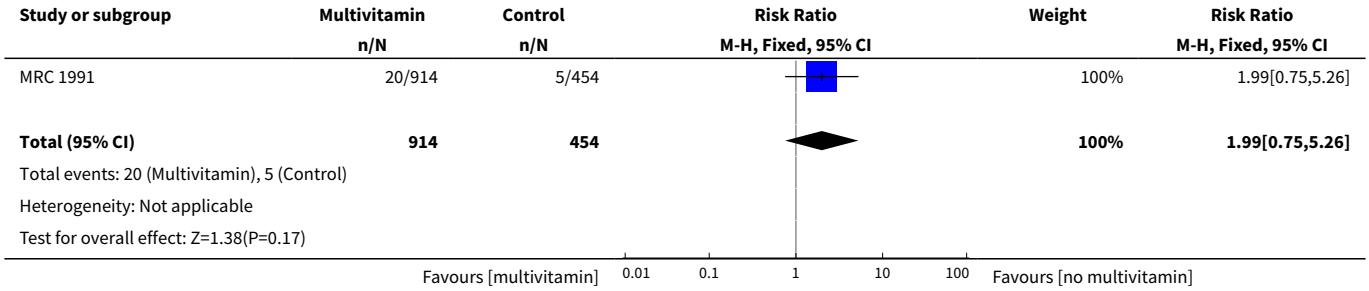
Analysis 11.2. Comparison 11 Multivitamin with/without folic acid versus no multivitamin/folic acid, Outcome 2 Early or late miscarriage.



Analysis 11.3. Comparison 11 Multivitamin with/without folic acid versus no multivitamin/folic acid, Outcome 3 Stillbirth.



Analysis 11.4. Comparison 11 Multivitamin with/without folic acid versus no multivitamin/folic acid, Outcome 4 Congenital malformations.



Comparison 12. Multivitamin plus folic acid versus folic acid

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Total fetal loss	3	5012	Risk Ratio (Fixed, 95% CI)	1.04 [0.88, 1.23]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2 Early or late miscarriage	3	5012	Risk Ratio (Fixed, 95% CI)	0.97 [0.80, 1.18]
3 Stillbirth	3	4316	Risk Ratio (Fixed, 95% CI)	1.32 [0.93, 1.88]
4 Congenital malformations	2	1096	Risk Ratio (M-H, Fixed, 95% CI)	1.71 [0.72, 4.04]

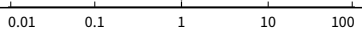
Analysis 12.1. Comparison 12 Multivitamin plus folic acid versus folic acid, Outcome 1 Total fetal loss.

Study or subgroup	Multivitamin N	Control N	log[Risk Ratio] (SE)	Risk Ratio IV, Fixed, 95% CI	Weight	Risk Ratio IV, Fixed, 95% CI
Kirke 1992	93	93	0 (0.448)		3.74%	1[0.42,2.41]
MRC 1991	461	449	0 (0.199)		18.96%	1.04[0.7,1.54]
Zeng 2008	1899	2017	0 (0.099)		77.3%	1.04[0.86,1.26]
Total (95% CI)					**100%**	**1.04[0.88,1.23]**
Heterogeneity: Tau^2=0; Chi^2=0.01, df=2(P=1); I^2=0%						
Test for overall effect: Z=0.43(P=0.67)						

Favours [multivitamin] Favours [folic acid]

Analysis 12.2. Comparison 12 Multivitamin plus folic acid versus folic acid, Outcome 2 Early or late miscarriage.

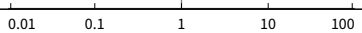
Study or subgroup	Multivitamin N	Control N	log[Risk Ratio] (SE)	Risk Ratio IV, Fixed, 95% CI	Weight	Risk Ratio IV, Fixed, 95% CI
Kirke 1992	93	93	0 (0.448)		5.11%	1[0.42,2.41]
MRC 1991	461	449	0 (0.204)		24.64%	1.04[0.7,1.56]
Zeng 2008	1899	2017	-0.1 (0.121)		70.26%	0.94[0.75,1.2]
Total (95% CI)					**100%**	**0.97[0.8,1.18]**
Heterogeneity: Tau^2=0; Chi^2=0.18, df=2(P=0.91); I^2=0%						
Test for overall effect: Z=0.29(P=0.77)						



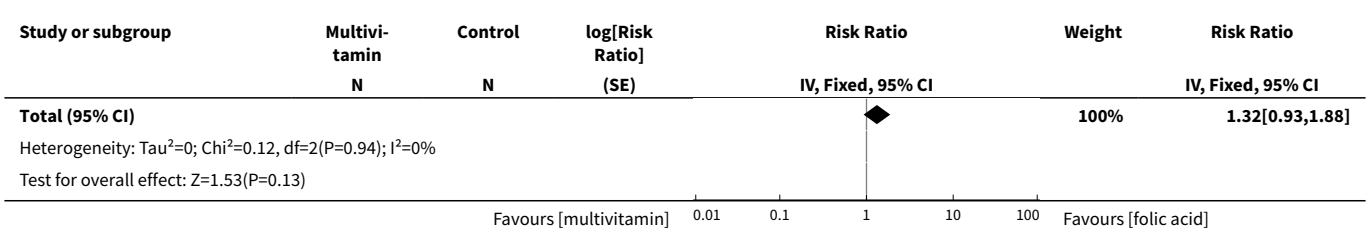
Favours [multivitamin] Favours [folic acid]

Analysis 12.3. Comparison 12 Multivitamin plus folic acid versus folic acid, Outcome 3 Stillbirth.

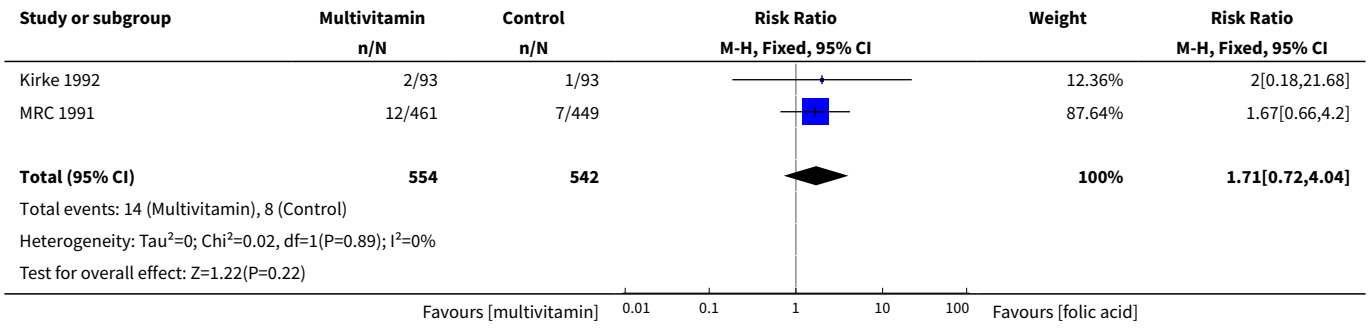
Study or subgroup	Multivitamin N	Control N	log[Risk Ratio] (SE)	Risk Ratio IV, Fixed, 95% CI	Weight	Risk Ratio IV, Fixed, 95% CI
Kirke 1992	93	93	0 (1.996)		0.82%	1[0.02,50]
MRC 1991	461	449	-0 (0.998)		3.26%	0.97[0.14,6.89]
Zeng 2008	1532	1688	0.3 (0.184)		95.92%	1.33[0.93,1.91]



Favours [multivitamin] Favours [folic acid]



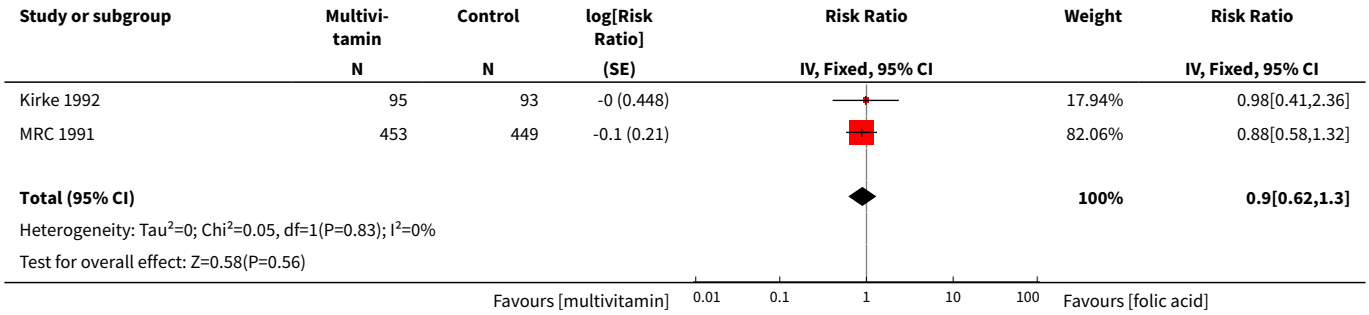
Analysis 12.4. Comparison 12 Multivitamin plus folic acid versus folic acid, Outcome 4 Congenital malformations.



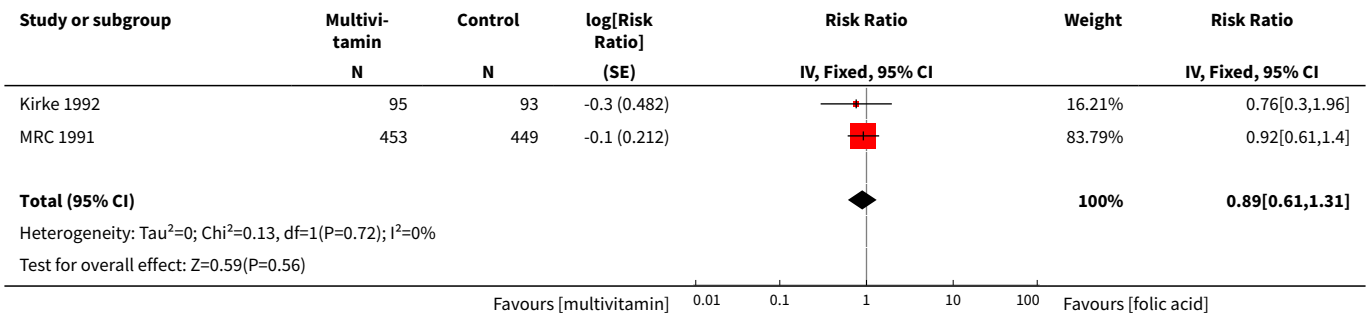
Comparison 13. Multivitamin without folic acid versus folic acid

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
1 Total fetal loss	2	1090	Risk Ratio (Fixed, 95% CI)	0.90 [0.62, 1.30]
2 Early or late miscarriage	2	1090	Risk Ratio (Fixed, 95% CI)	0.89 [0.61, 1.31]
3 Stillbirth	2	1090	Risk Ratio (Random, 95% CI)	0.99 [0.04, 22.90]
4 Congenital malformations	2	1090	Risk Ratio (M-H, Fixed, 95% CI)	1.61 [0.67, 3.85]

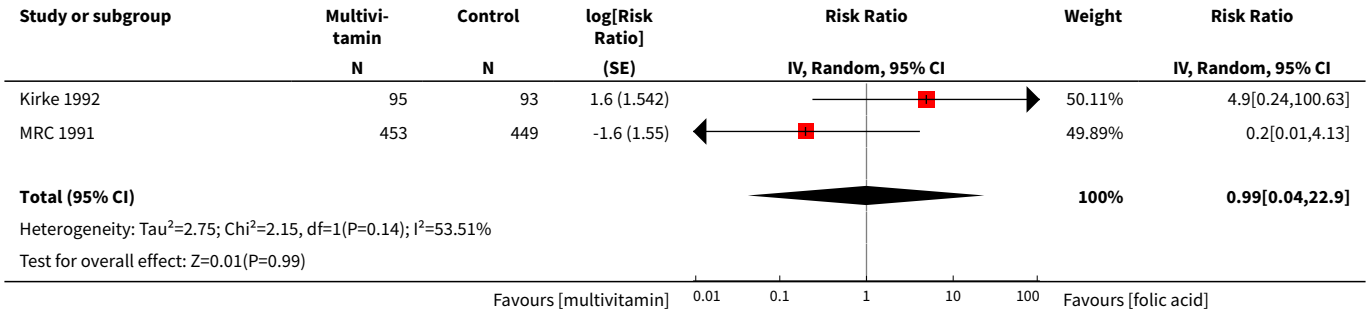
Analysis 13.1. Comparison 13 Multivitamin without folic acid versus folic acid, Outcome 1 Total fetal loss.



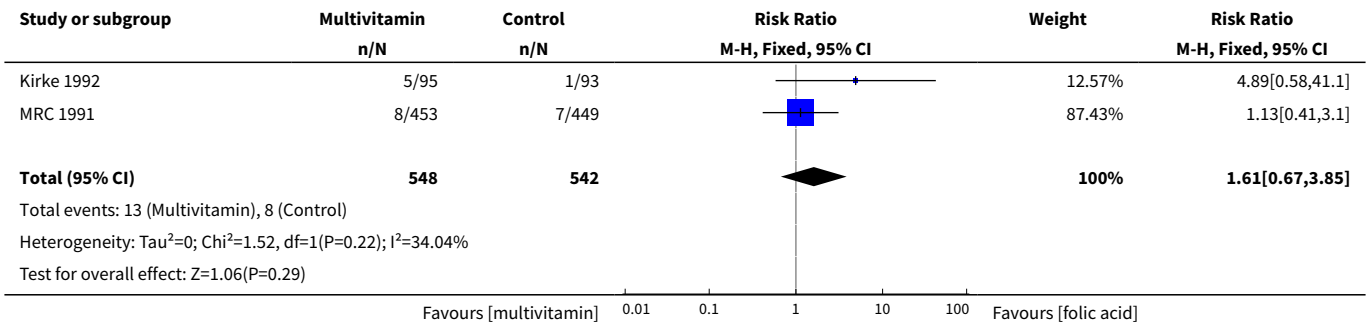
Analysis 13.2. Comparison 13 Multivitamin without folic acid versus folic acid, Outcome 2 Early or late miscarriage.



Analysis 13.3. Comparison 13 Multivitamin without folic acid versus folic acid, Outcome 3 Stillbirth.



Analysis 13.4. Comparison 13 Multivitamin without folic acid versus folic acid, Outcome 4 Congenital malformations.



Comparison 14. Multivitamin with/without folic acid versus folic acid

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Total fetal loss	2	1644	Risk Ratio (Fixed, 95% CI)	0.96 [0.70, 1.33]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2 Early of late miscarriage	2	1644	Risk Ratio (Fixed, 95% CI)	0.96 [0.70, 1.33]
3 Stillbirth	2	1644	Risk Ratio (Fixed, 95% CI)	0.79 [0.15, 4.10]
4 Congenital malformations	2	1644	Risk Ratio (M-H, Fixed, 95% CI)	1.66 [0.76, 3.63]

Analysis 14.1. Comparison 14 Multivitamin with/without folic acid versus folic acid, Outcome 1 Total fetal loss.

Study or subgroup	Multivitamin N	Control N	log[Risk Ratio] (SE)	Risk Ratio IV, Fixed, 95% CI	Weight	Risk Ratio IV, Fixed, 95% CI
Kirke 1992	188	93	-0 (0.448)		13.38%	0.98[0.41,2.36]
MRC 1991	914	449	-0 (0.176)		86.62%	0.96[0.68,1.36]
Total (95% CI)					**100%**	**0.96[0.7,1.33]**
Heterogeneity: Tau²=0; Chi²=0, df=1(P=0.97); I²=0%						
Test for overall effect: Z=0.23(P=0.82)						

Favours [multivitamin] Favours [folic acid]

Analysis 14.2. Comparison 14 Multivitamin with/without folic acid versus folic acid, Outcome 2 Early of late miscarriage.

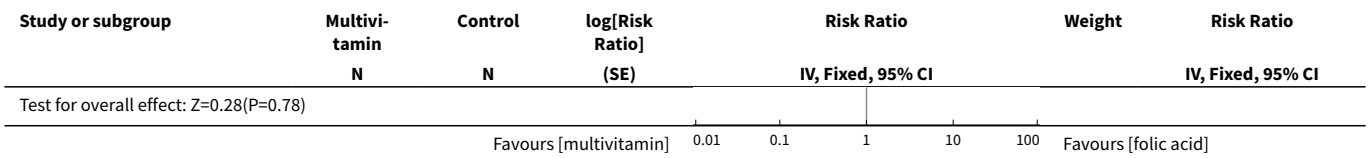
Study or subgroup	Multivitamin N	Control N	log[Risk Ratio] (SE)	Risk Ratio IV, Fixed, 95% CI	Weight	Risk Ratio IV, Fixed, 95% CI
Kirke 1992	188	93	-0.1 (0.397)		17.06%	0.88[0.4,1.91]
MRC 1991	914	449	-0 (0.18)		82.94%	0.98[0.69,1.4]
Total (95% CI)					**100%**	**0.96[0.7,1.33]**
Heterogeneity: Tau²=0; Chi²=0.06, df=1(P=0.8); I²=0%						
Test for overall effect: Z=0.22(P=0.82)						

Favours [multivitamin] Favours [folic acid]

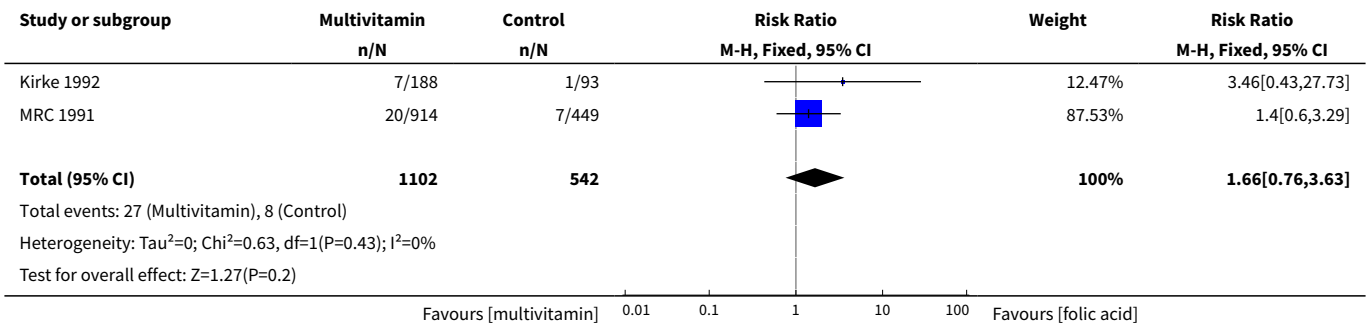
Analysis 14.3. Comparison 14 Multivitamin with/without folic acid versus folic acid, Outcome 3 Stillbirth.

Study or subgroup	Multivitamin N	Control N	log[Risk Ratio] (SE)	Risk Ratio IV, Fixed, 95% CI	Weight	Risk Ratio IV, Fixed, 95% CI
Kirke 1992	188	93	0.9 (1.544)		29.49%	2.49[0.12,51.27]
MRC 1991	914	449	-0.7 (0.999)		70.51%	0.49[0.07,3.48]
Total (95% CI)					**100%**	**0.79[0.15,4.1]**
Heterogeneity: Tau²=0; Chi²=0.78, df=1(P=0.38); I²=0%						

Favours [multivitamin] Favours [folic acid]



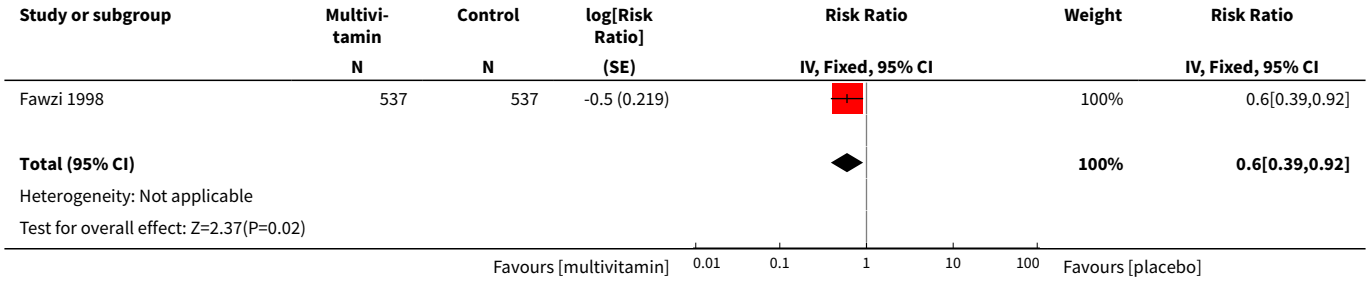
Analysis 14.4. Comparison 14 Multivitamin with/without folic acid versus folic acid, Outcome 4 Congenital malformations.



Comparison 15. Multivitamin with/without vitamin A versus vitamin A or placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Total fetal loss	1	1074	Risk Ratio (Fixed, 95% CI)	0.60 [0.39, 0.92]

Analysis 15.1. Comparison 15 Multivitamin with/without vitamin A versus vitamin A or placebo, Outcome 1 Total fetal loss.

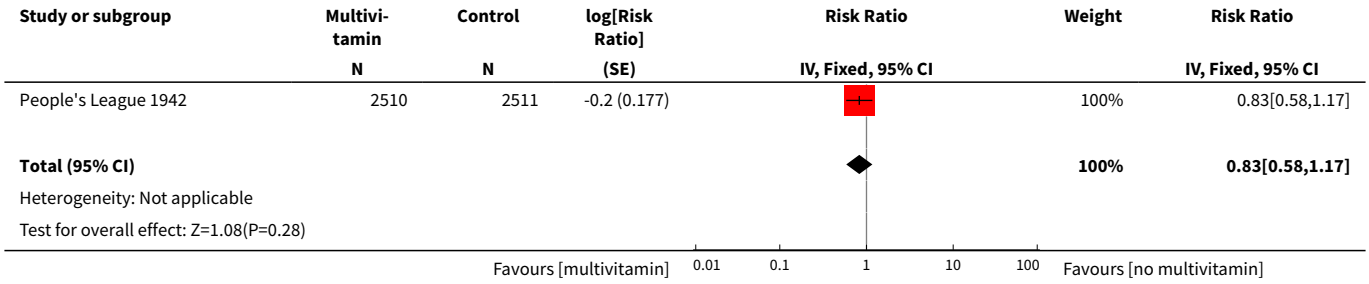


Comparison 16. Multivitamin versus control

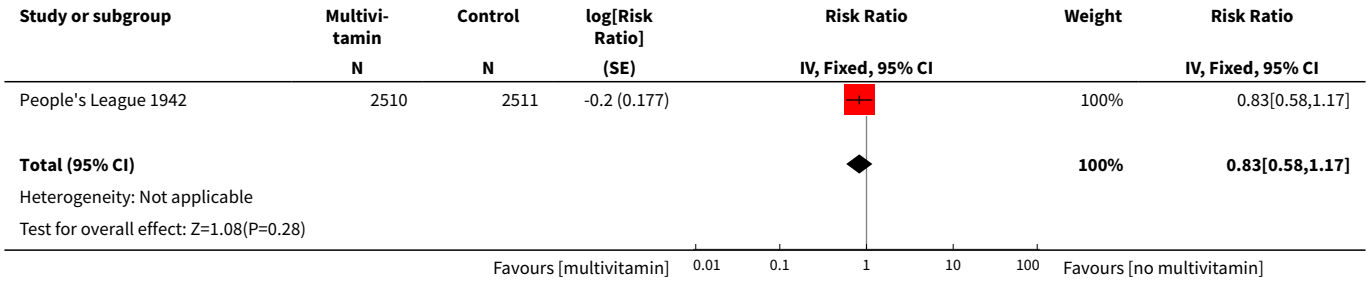
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Total fetal loss	1	5021	Risk Ratio (Fixed, 95% CI)	0.83 [0.58, 1.17]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2 Stillbirth	1	5021	Risk Ratio (Fixed, 95% CI)	0.83 [0.58, 1.17]

Analysis 16.1. Comparison 16 Multivitamin versus control, Outcome 1 Total fetal loss.



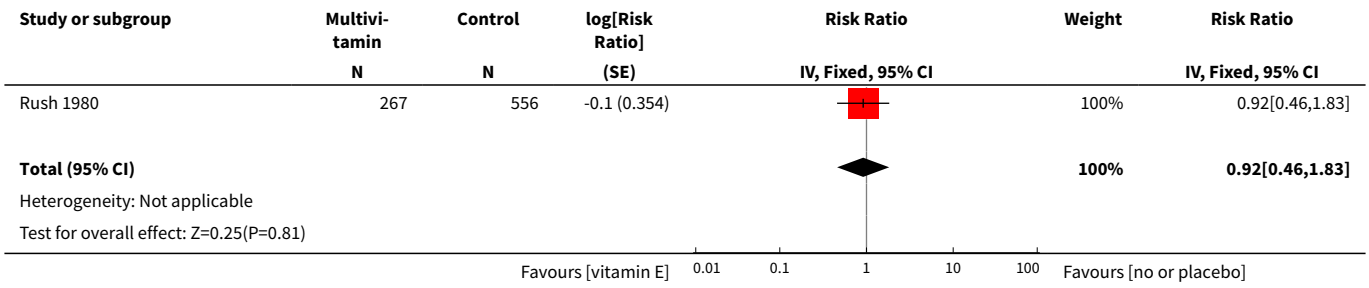
Analysis 16.2. Comparison 16 Multivitamin versus control, Outcome 2 Stillbirth.



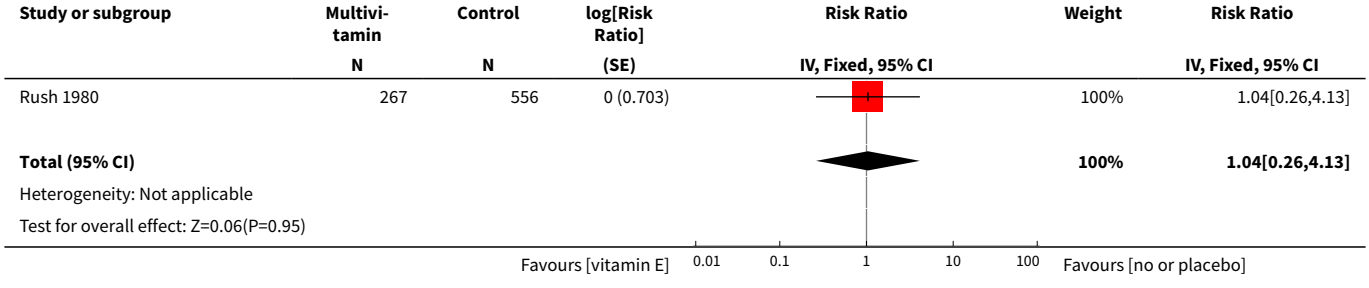
Comparison 17. Multivitamin plus vitamin E versus multivitamin without vitamin E or control

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Total fetal loss	1	823	Risk Ratio (Fixed, 95% CI)	0.92 [0.46, 1.83]
2 Early or late miscarriage	1	823	Risk Ratio (Fixed, 95% CI)	1.04 [0.26, 4.13]
3 Stillbirth	1	823	Risk Ratio (Fixed, 95% CI)	0.88 [0.39, 1.98]

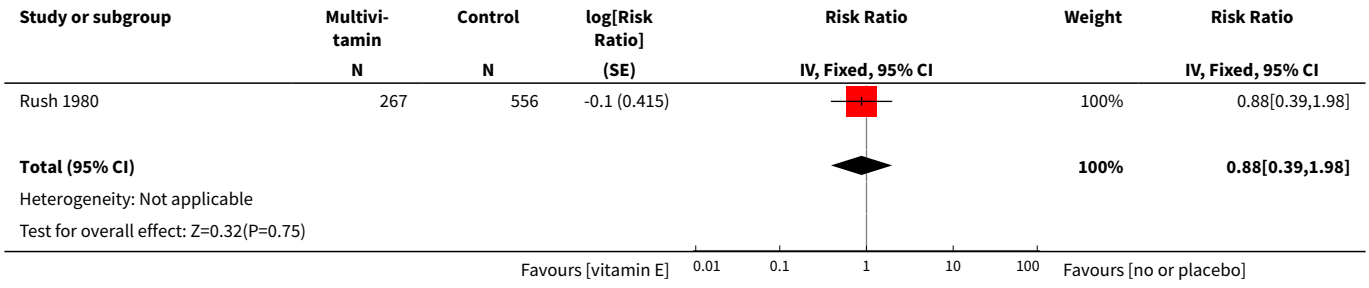
Analysis 17.1. Comparison 17 Multivitamin plus vitamin E versus multivitamin without vitamin E or control, Outcome 1 Total fetal loss.



Analysis 17.2. Comparison 17 Multivitamin plus vitamin E versus multivitamin without vitamin E or control, Outcome 2 Early or late miscarriage.



Analysis 17.3. Comparison 17 Multivitamin plus vitamin E versus multivitamin without vitamin E or control, Outcome 3 Stillbirth.



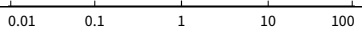
Comparison 18. Multivitamin plus folic acid versus no multivitamin/folic acid

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Total fetal loss	3	6883	Risk Ratio (Random, 95% CI)	1.00 [0.75, 1.34]
2 Early or late miscarriage	3	6883	Risk Ratio (Random, 95% CI)	0.99 [0.72, 1.38]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3 Stillbirth	3	6883	Risk Ratio (Fixed, 95% CI)	1.04 [0.51, 2.10]
4 Congenital malformations	2	5777	Risk Ratio (M-H, Fixed, 95% CI)	1.69 [0.81, 3.53]

Analysis 18.1. Comparison 18 Multivitamin plus folic acid versus no multivitamin/folic acid, Outcome 1 Total fetal loss.

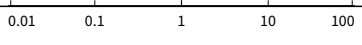
Study or subgroup	Multivitamin N	Control N	log[Risk Ratio] (SE)	Risk Ratio IV, Random, 95% CI	Weight	Risk Ratio IV, Random, 95% CI
Czeizel 1994	2819	2683	0.1 (0.08)		57.85%	1.14[0.98,1.33]
ICMR 2000	231	235	-0.6 (0.402)		11.11%	0.54[0.25,1.18]
MRC 1991	461	454	-0 (0.195)		31.03%	0.98[0.67,1.44]
Total (95% CI)					**100%**	**1[0.75,1.34]**
Heterogeneity: Tau^2=0.03; Chi^2=3.69, df=2(P=0.16); I^2=45.86%						
Test for overall effect: Z=0.02(P=0.98)						



Favours [multivitamin] Favours [no multivitamin]

Analysis 18.2. Comparison 18 Multivitamin plus folic acid versus no multivitamin/folic acid, Outcome 2 Early or late miscarriage.

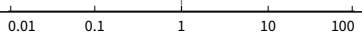
Study or subgroup	Multivitamin N	Control N	log[Risk Ratio] (SE)	Risk Ratio IV, Random, 95% CI	Weight	Risk Ratio IV, Random, 95% CI
Czeizel 1994	2819	2683	0.1 (0.081)		56.42%	1.14[0.97,1.34]
ICMR 2000	231	235	-0.8 (0.479)		10.21%	0.44[0.17,1.11]
MRC 1991	461	454	0 (0.201)		33.38%	1.01[0.68,1.49]
Total (95% CI)					**100%**	**0.99[0.72,1.38]**
Heterogeneity: Tau^2=0.04; Chi^2=4.13, df=2(P=0.13); I^2=51.56%						
Test for overall effect: Z=0.05(P=0.96)						



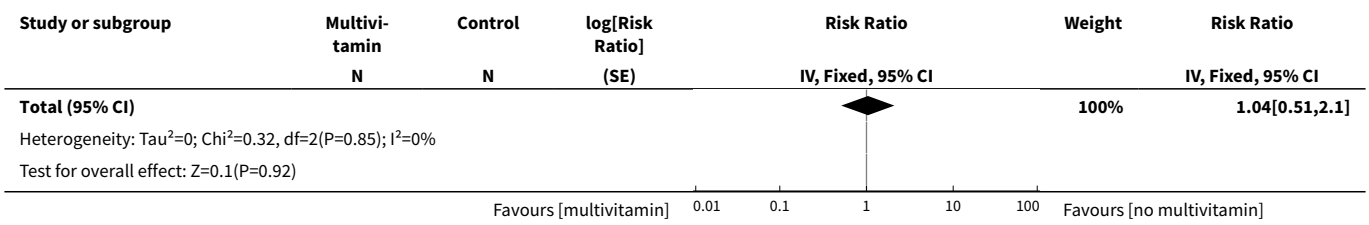
Favours [multivitamin] Favours [no multivitamin]

Analysis 18.3. Comparison 18 Multivitamin plus folic acid versus no multivitamin/folic acid, Outcome 3 Stillbirth.

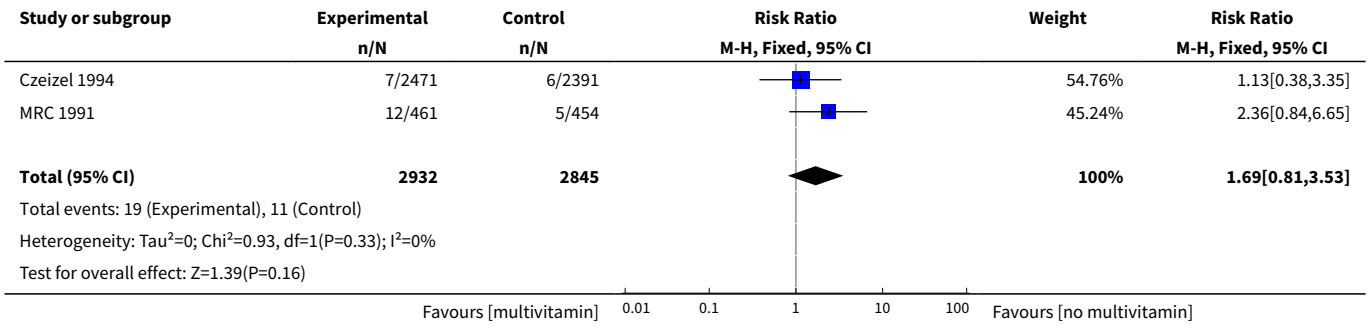
Study or subgroup	Multivitamin N	Control N	log[Risk Ratio] (SE)	Risk Ratio IV, Fixed, 95% CI	Weight	Risk Ratio IV, Fixed, 95% CI
Czeizel 1994	2819	2683	0.2 (0.449)		64.56%	1.16[0.48,2.8]
ICMR 2000	231	235	0 (0.811)		19.76%	1.02[0.21,4.99]
MRC 1991	461	454	-0.4 (0.911)		15.68%	0.66[0.11,3.91]



Favours [multivitamin] Favours [no multivitamin]



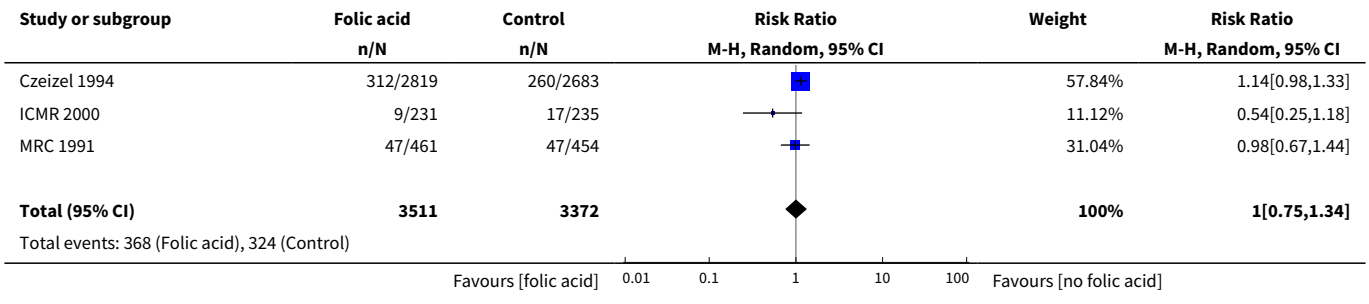
Analysis 18.4. Comparison 18 Multivitamin plus folic acid versus no multivitamin/folic acid, Outcome 4 Congenital malformations.



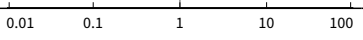
Comparison 19. Folic acid plus multivitamin versus no folic acid/multivitamin

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
1 Total fetal loss	3	6883	Risk Ratio (M-H, Random, 95% CI)	1.00 [0.75, 1.34]
2 Early or late miscarriage	3	6883	Risk Ratio (M-H, Random, 95% CI)	0.99 [0.72, 1.38]
3 Stillbirth	3	6883	Risk Ratio (M-H, Fixed, 95% CI)	1.03 [0.51, 2.09]
4 Congenital malformations	2	5777	Risk Ratio (M-H, Fixed, 95% CI)	1.69 [0.81, 3.53]

Analysis 19.1. Comparison 19 Folic acid plus multivitamin versus no folic acid/multivitamin, Outcome 1 Total fetal loss.

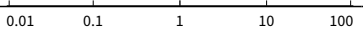


Study or subgroup	Folic acid n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Heterogeneity: Tau²=0.03; Chi²=3.7, df=2(P=0.16); I²=45.89%					
Test for overall effect: Z=0.02(P=0.98)					



Analysis 19.2. Comparison 19 Folic acid plus multivitamin versus no folic acid/multivitamin, Outcome 2 Early or late miscarriage.

Study or subgroup	Folic acid n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Czeizel 1994	301/2819	251/2683		56.4%	1.14[0.97,1.34]
ICMR 2000	6/231	14/235		10.21%	0.44[0.17,1.11]
MRC 1991	45/461	44/454		33.38%	1.01[0.68,1.49]
Total (95% CI)	**3511**	**3372**		**100%**	**0.99[0.72,1.38]**
Total events: 352 (Folic acid), 309 (Control)					
Heterogeneity: Tau²=0.04; Chi²=4.13, df=2(P=0.13); I²=51.59%					
Test for overall effect: Z=0.05(P=0.96)					

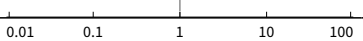


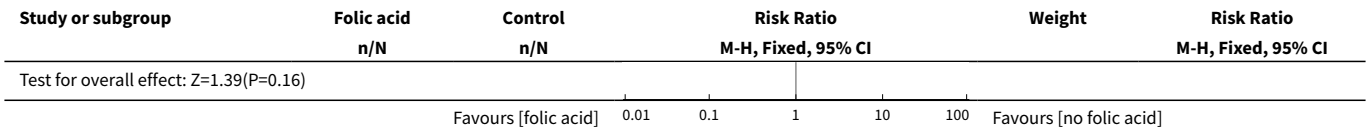
Analysis 19.3. Comparison 19 Folic acid plus multivitamin versus no folic acid/multivitamin, Outcome 3 Stillbirth.

Study or subgroup	Folic acid n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Czeizel 1994	11/2819	9/2683		60.6%	1.16[0.48,2.8]
ICMR 2000	3/231	3/235		19.54%	1.02[0.21,4.99]
MRC 1991	2/461	3/454		19.86%	0.66[0.11,3.91]
Total (95% CI)	**3511**	**3372**		**100%**	**1.03[0.51,2.09]**
Total events: 16 (Folic acid), 15 (Control)					
Heterogeneity: Tau²=0; Chi²=0.32, df=2(P=0.85); I²=0%					
Test for overall effect: Z=0.09(P=0.93)					

Analysis 19.4. Comparison 19 Folic acid plus multivitamin versus no folic acid/multivitamin, Outcome 4 Congenital malformations.

Study or subgroup	Folic acid n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Czeizel 1994	7/2471	6/2391		54.76%	1.13[0.38,3.35]
MRC 1991	12/461	5/454		45.24%	2.36[0.84,6.65]
Total (95% CI)	**2932**	**2845**		**100%**	**1.69[0.81,3.53]**
Total events: 19 (Folic acid), 11 (Control)					
Heterogeneity: Tau²=0; Chi²=0.93, df=1(P=0.33); I²=0%					

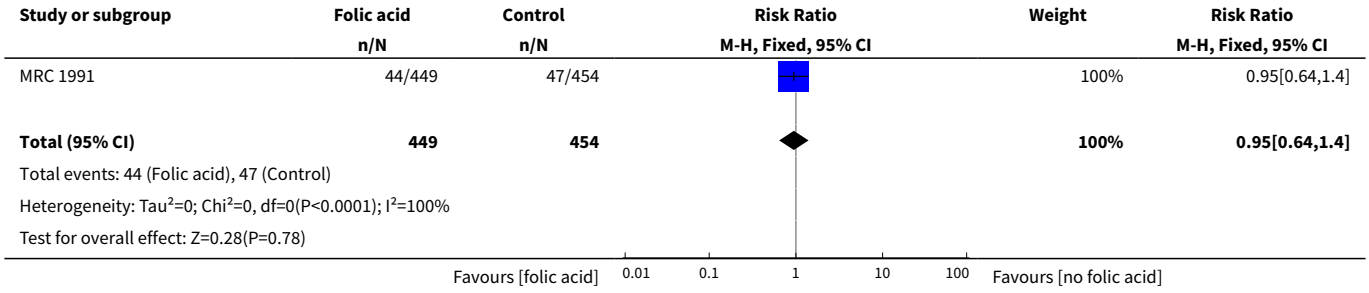




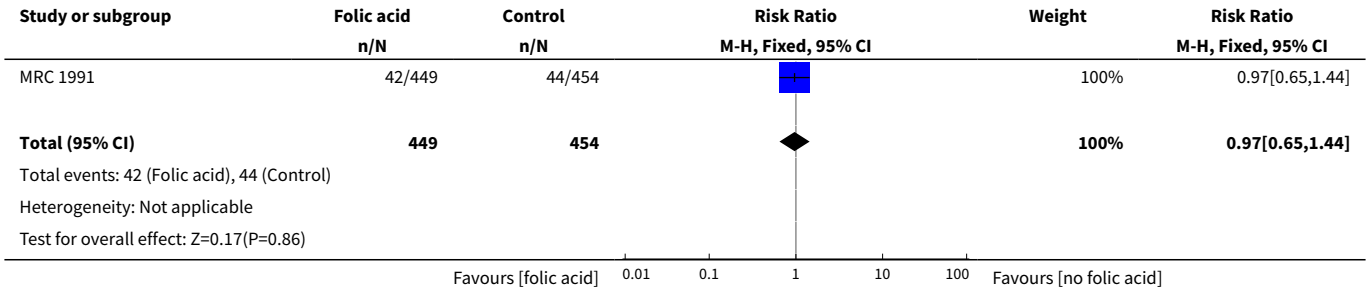
Comparison 20. Folic acid without multivitamin versus no folic acid/multivitamin

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Total fetal loss	1	903	Risk Ratio (M-H, Fixed, 95% CI)	0.95 [0.64, 1.40]
2 Early or late miscarriage	1	903	Risk Ratio (M-H, Fixed, 95% CI)	0.97 [0.65, 1.44]
3 Stillbirth	1	903	Risk Ratio (M-H, Fixed, 95% CI)	0.67 [0.11, 4.02]
4 Congenital malformations	1	903	Risk Ratio (M-H, Fixed, 95% CI)	1.42 [0.45, 4.43]

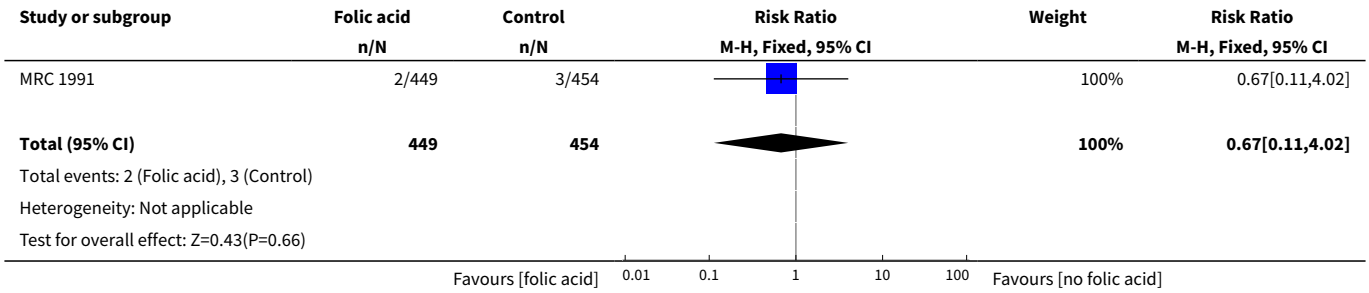
Analysis 20.1. Comparison 20 Folic acid without multivitamin versus no folic acid/multivitamin, Outcome 1 Total fetal loss.



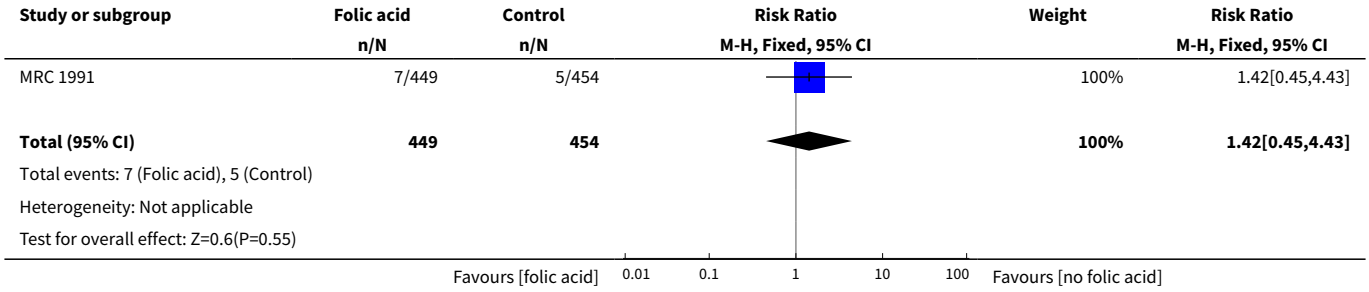
Analysis 20.2. Comparison 20 Folic acid without multivitamin versus no folic acid/multivitamin, Outcome 2 Early or late miscarriage.



Analysis 20.3. Comparison 20 Folic acid without multivitamin versus no folic acid/multivitamin, Outcome 3 Stillbirth.



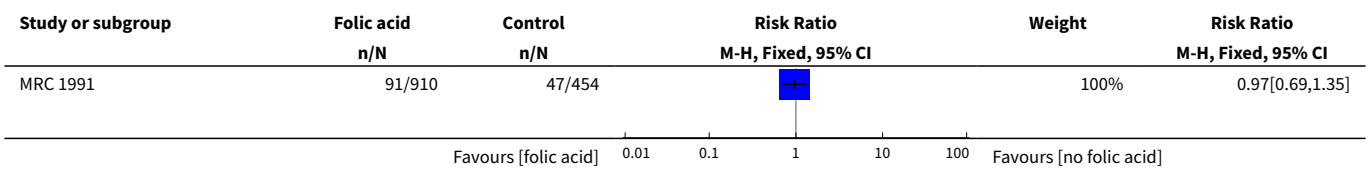
Analysis 20.4. Comparison 20 Folic acid without multivitamin versus no folic acid/multivitamin, Outcome 4 Congenital malformations.

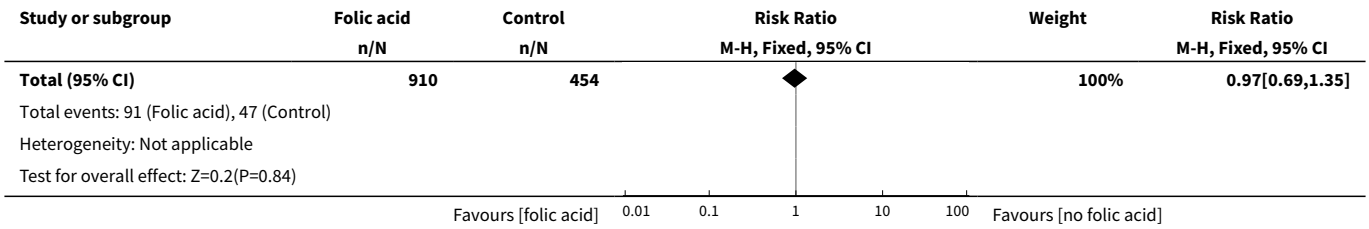


Comparison 21. Folic acid with/without multivitamin versus no folic acid/multivitamin

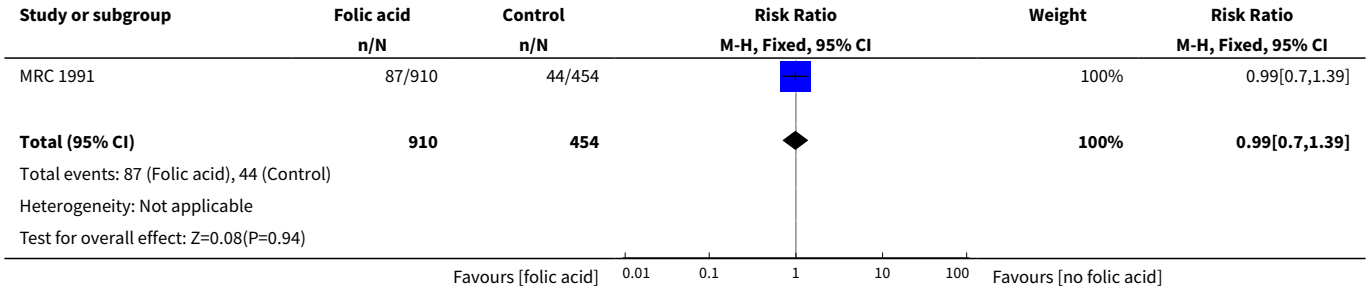
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Total fetal loss	1	1364	Risk Ratio (M-H, Fixed, 95% CI)	0.97 [0.69, 1.35]
2 Early or late miscarriage	1	1364	Risk Ratio (M-H, Fixed, 95% CI)	0.99 [0.70, 1.39]
3 Stillbirth	1	1364	Risk Ratio (M-H, Fixed, 95% CI)	0.67 [0.15, 2.96]
4 Congenital malformations	1	1364	Risk Ratio (M-H, Fixed, 95% CI)	1.90 [0.71, 5.04]

Analysis 21.1. Comparison 21 Folic acid with/without multivitamin versus no folic acid/multivitamin, Outcome 1 Total fetal loss.

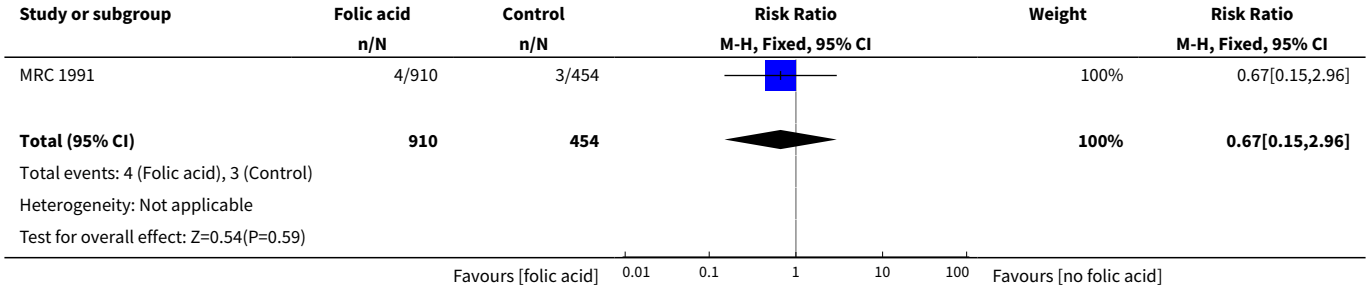




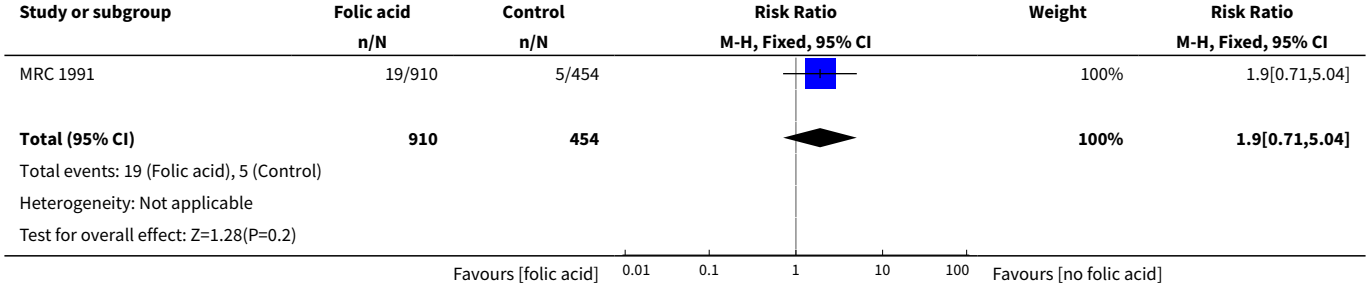
Analysis 21.2. Comparison 21 Folic acid with/without multivitamin versus no folic acid/multivitamin, Outcome 2 Early or late miscarriage.



Analysis 21.3. Comparison 21 Folic acid with/without multivitamin versus no folic acid/multivitamin, Outcome 3 Stillbirth.



Analysis 21.4. Comparison 21 Folic acid with/without multivitamin versus no folic acid/multivitamin, Outcome 4 Congenital malformations.



Comparison 22. Folic acis plus multivitamin versus multivitamin

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
1 Total fetal loss	2	1102	Risk Ratio (M-H, Fixed, 95% CI)	1.15 [0.80, 1.67]
2 Early or late miscarriage	2	1102	Risk Ratio (M-H, Fixed, 95% CI)	1.16 [0.80, 1.69]
3 Stillbirth	2	1102	Risk Ratio (M-H, Random, 95% CI)	1.00 [0.04, 22.55]
4 Congenital malformations	2	1102	Risk Ratio (M-H, Random, 95% CI)	0.93 [0.28, 3.12]

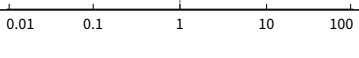
Analysis 22.1. Comparison 22 Folic acis plus multivitamin versus multivitamin, Outcome 1 Total fetal loss.

Study or subgroup	Folic acid n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Kirke 1992	9/93	9/95		18.46%	1.02[0.42,2.46]
MRC 1991	47/461	39/453		81.54%	1.18[0.79,1.77]
Total (95% CI)	**554**	**548**		**100%**	**1.15[0.8,1.67]**
Total events: 56 (Folic acid), 48 (Control)					
Heterogeneity: Tau^2=0; Chi^2=0.09, df=1(P=0.76); I^2=0%					
Test for overall effect: Z=0.77(P=0.44)					

Favours [folic acid] Favours [multivitamin]

Analysis 22.2. Comparison 22 Folic acis plus multivitamin versus multivitamin, Outcome 2 Early or late miscarriage.

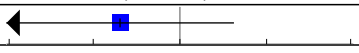
Study or subgroup	Folic acid n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Kirke 1992	9/93	7/95		14.97%	1.31[0.51,3.38]
MRC 1991	45/461	39/453		85.03%	1.13[0.75,1.71]
Total (95% CI)	**554**	**548**		**100%**	**1.16[0.8,1.69]**
Total events: 54 (Folic acid), 46 (Control)					
Heterogeneity: Tau^2=0; Chi^2=0.08, df=1(P=0.78); I^2=0%					
Test for overall effect: Z=0.78(P=0.44)					



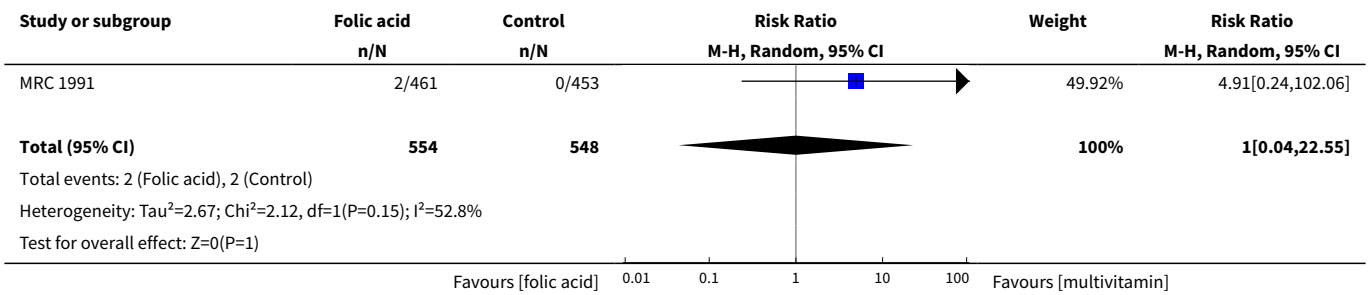
Favours [folic acid] Favours [multivitamin]

Analysis 22.3. Comparison 22 Folic acis plus multivitamin versus multivitamin, Outcome 3 Stillbirth.

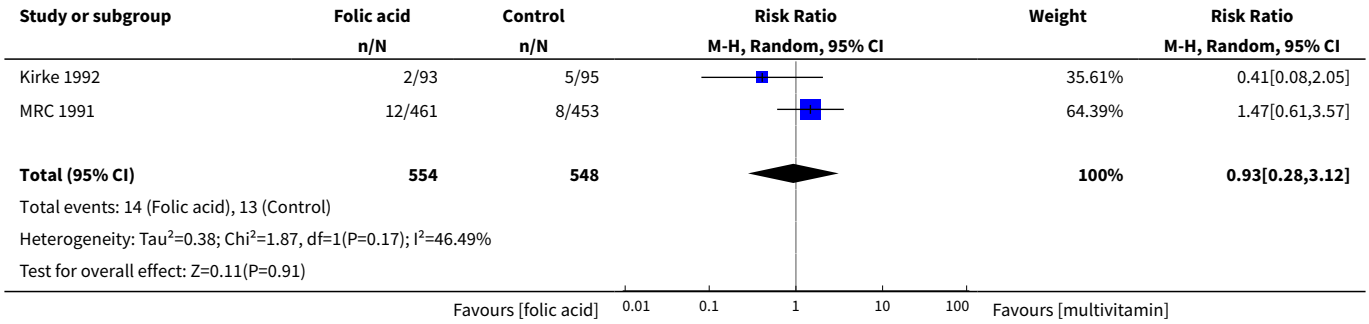
Study or subgroup	Folic acid n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Kirke 1992	0/93	2/95		50.08%	0.2[0.01,4.2]



Favours [folic acid] Favours [multivitamin]



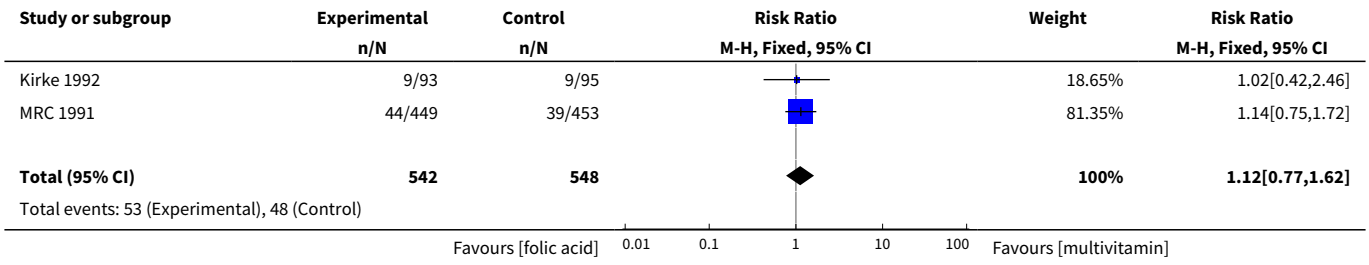
Analysis 22.4. Comparison 22 Folic acis plus multivitamin versus multivitamin, Outcome 4 Congenital malformations.

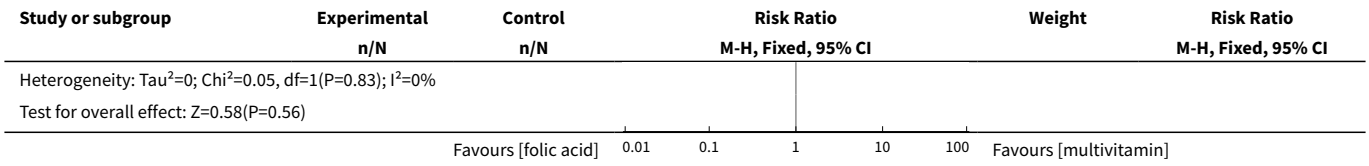


Comparison 23. Folic acid without multivitamin versus multivitamin

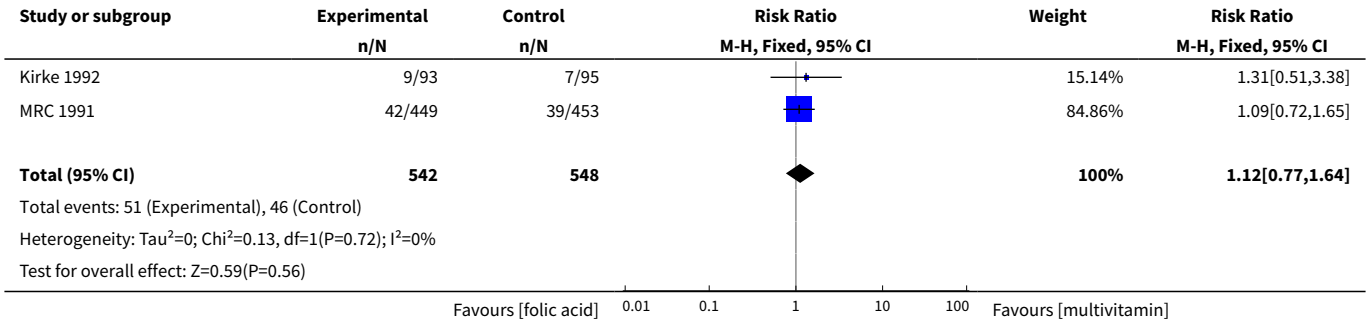
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Total fetal loss	2	1090	Risk Ratio (M-H, Fixed, 95% CI)	1.12 [0.77, 1.62]
2 Early or late miscarriage	2	1090	Risk Ratio (M-H, Fixed, 95% CI)	1.12 [0.77, 1.64]
3 Stillbirth	2	1090	Risk Ratio (M-H, Fixed, 95% CI)	4.97 [0.58, 42.29]
4 Congenital malformations	2	1090	Risk Ratio (M-H, Fixed, 95% CI)	0.62 [0.26, 1.49]

Analysis 23.1. Comparison 23 Folic acid without multivitamin versus multivitamin, Outcome 1 Total fetal loss.

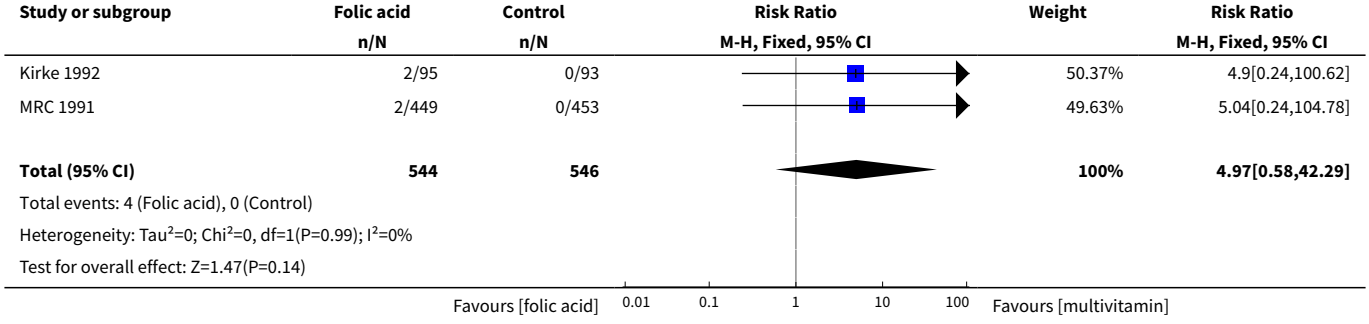




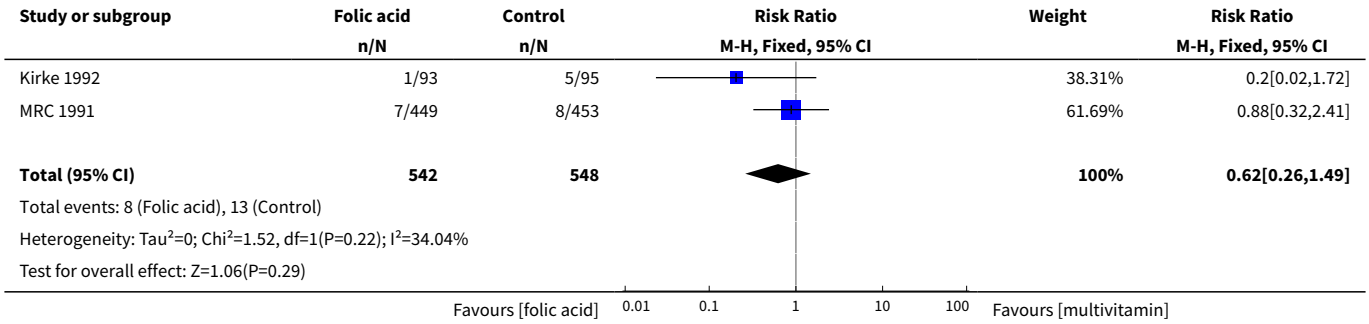
Analysis 23.2. Comparison 23 Folic acid without multivitamin versus multivitamin, Outcome 2 Early or late miscarriage.



Analysis 23.3. Comparison 23 Folic acid without multivitamin versus multivitamin, Outcome 3 Stillbirth.



Analysis 23.4. Comparison 23 Folic acid without multivitamin versus multivitamin, Outcome 4 Congenital malformations.

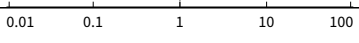


Comparison 24. Folic acid with or without multivitamin versus multivitamin

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Total fetal loss	2	1644	Risk Ratio (M-H, Fixed, 95% CI)	1.14 [0.82, 1.57]
2 Early or late miscarriage	2	1642	Risk Ratio (M-H, Fixed, 95% CI)	1.09 [0.79, 1.51]
3 Stillbirth	2	1644	Risk Ratio (M-H, Random, 95% CI)	0.69 [0.02, 28.39]
4 Congenital malformations	2	1644	Risk Ratio (M-H, Random, 95% CI)	0.68 [0.19, 2.51]

Analysis 24.1. Comparison 24 Folic acid with or without multivitamin versus multivitamin, Outcome 1 Total fetal loss.

Study or subgroup	Folic acid n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Kirke 1992	18/186	9/95		18.62%	1.02[0.48,2.19]
MRC 1991	91/910	39/453		81.38%	1.16[0.81,1.66]
Total (95% CI)	**1096**	**548**		**100%**	**1.14[0.82,1.57]**
Total events: 109 (Folic acid), 48 (Control)					
Heterogeneity: Tau^2=0; Chi^2=0.09, df=1(P=0.76); I^2=0%					
Test for overall effect: Z=0.77(P=0.44)					



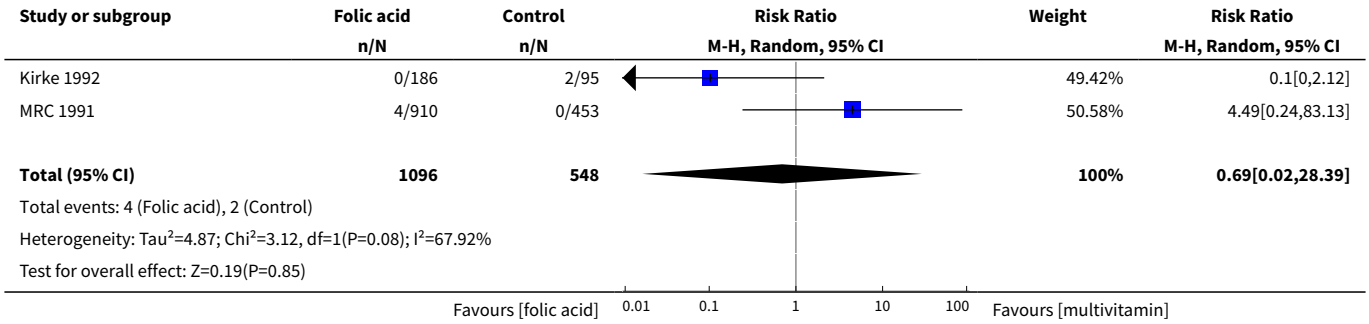
Favours [folic acid] Favours [multivitamin]

Analysis 24.2. Comparison 24 Folic acid with or without multivitamin versus multivitamin, Outcome 2 Early or late miscarriage.

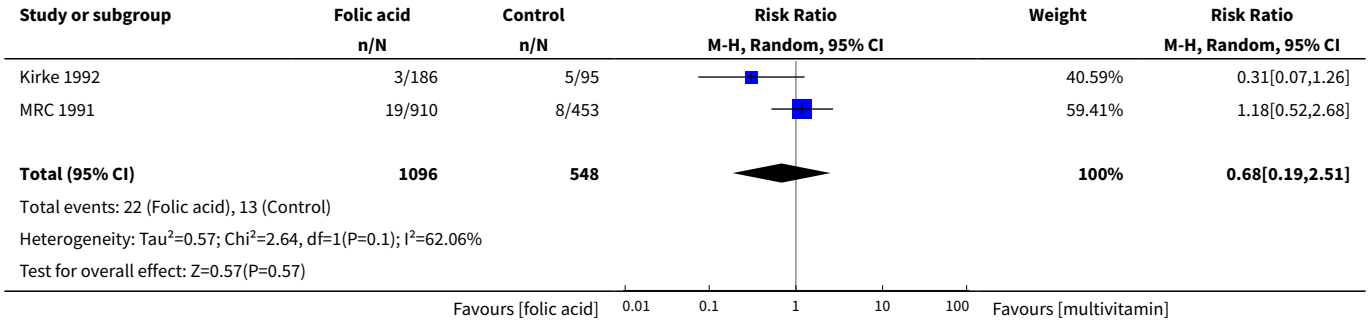
Study or subgroup	Folic acid n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Kirke 1992	18/186	9/93		18.73%	1[0.47,2.14]
MRC 1991	87/910	39/453		81.27%	1.11[0.77,1.59]
Total (95% CI)	**1096**	**546**		**100%**	**1.09[0.79,1.51]**
Total events: 105 (Folic acid), 48 (Control)					
Heterogeneity: Tau^2=0; Chi^2=0.06, df=1(P=0.81); I^2=0%					
Test for overall effect: Z=0.52(P=0.6)					

Favours [folic acid] Favours [multivitamin]

Analysis 24.3. Comparison 24 Folic acid with or without multivitamin versus multivitamin, Outcome 3 Stillbirth.



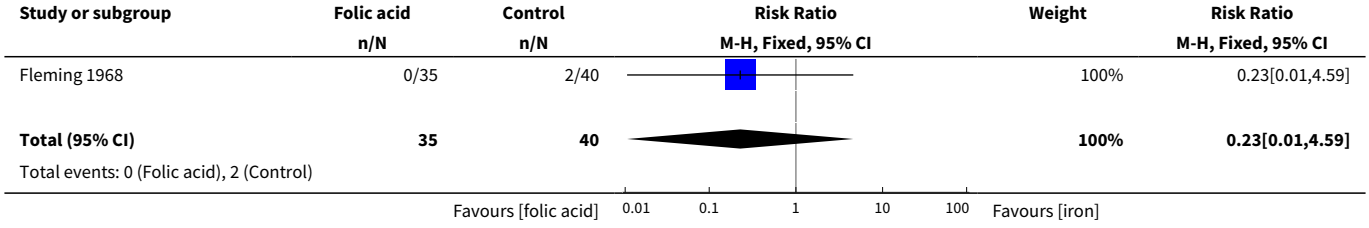
Analysis 24.4. Comparison 24 Folic acid with or without multivitamin versus multivitamin, Outcome 4 Congenital malformations.

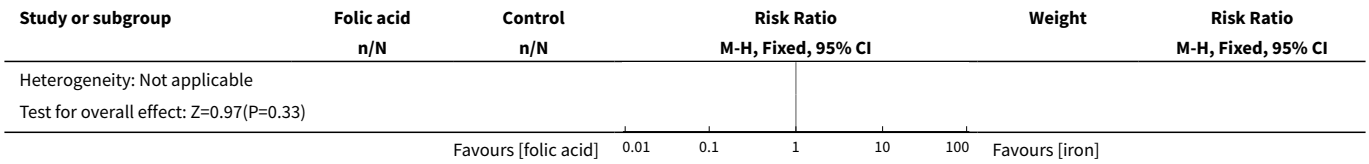


Comparison 25. Folic acid plus iron versus iron

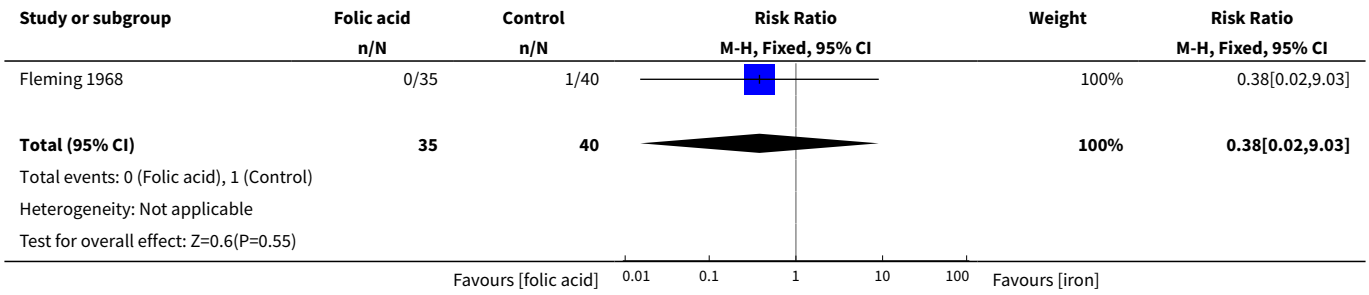
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Total fetal loss	1	75	Risk Ratio (M-H, Fixed, 95% CI)	0.23 [0.01, 4.59]
2 Early or late miscarriage	1	75	Risk Ratio (M-H, Fixed, 95% CI)	0.38 [0.02, 9.03]
3 Stillbirth	1	75	Risk Ratio (M-H, Fixed, 95% CI)	0.38 [0.02, 9.03]

Analysis 25.1. Comparison 25 Folic acid plus iron versus iron, Outcome 1 Total fetal loss.

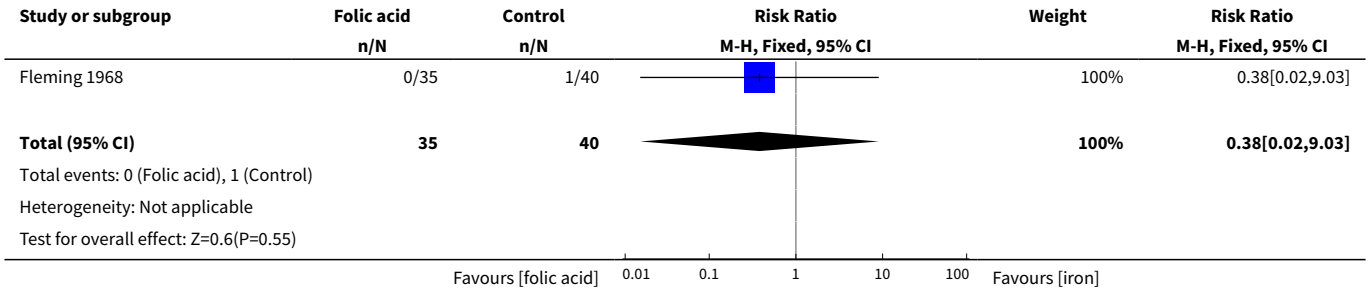




Analysis 25.2. Comparison 25 Folic acid plus iron versus iron, Outcome 2 Early or late miscarriage.



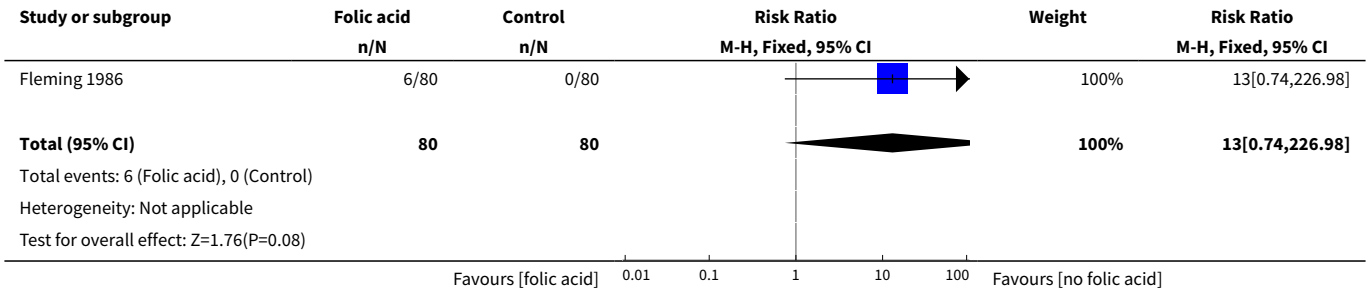
Analysis 25.3. Comparison 25 Folic acid plus iron versus iron, Outcome 3 Stillbirth.



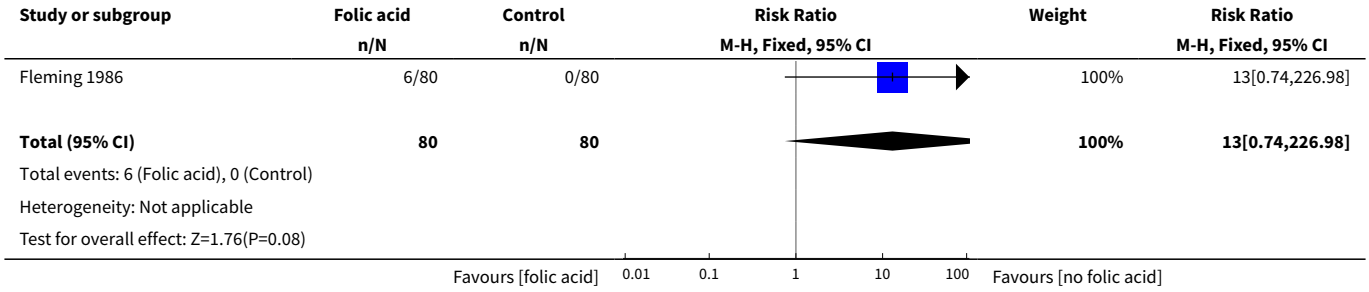
Comparison 26. Folic acid plus iron and antimalarials versus iron and antimalarials

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Total fetal loss	1	160	Risk Ratio (M-H, Fixed, 95% CI)	13.0 [0.74, 226.98]
2 Early or late miscarriage	1	160	Risk Ratio (M-H, Fixed, 95% CI)	13.0 [0.74, 226.98]

Analysis 26.1. Comparison 26 Folic acid plus iron and antimalarials versus iron and antimalarials, Outcome 1 Total fetal loss.



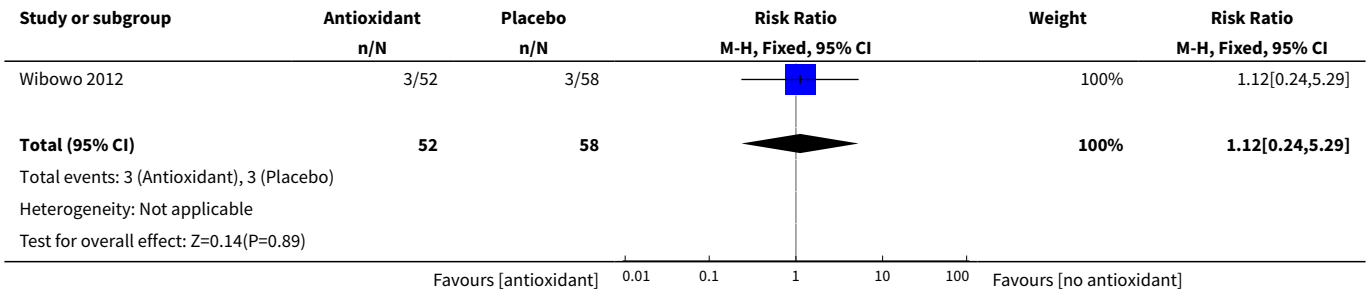
Analysis 26.2. Comparison 26 Folic acid plus iron and antimalarials versus iron and antimalarials, Outcome 2 Early or late miscarriage.



Comparison 27. Antioxidant vitamin supplementation

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Early or late miscarriage	1	110	Risk Ratio (M-H, Fixed, 95% CI)	1.12 [0.24, 5.29]

Analysis 27.1. Comparison 27 Antioxidant vitamin supplementation, Outcome 1 Early or late miscarriage.



APPENDICES

Appendix 1. Additional searching carried out for the initial version of the review

For the initial version of the review, authors carried out a separate search of CENTRAL *(The Cochrane Library,* 2003, Issue 2) for the following terms: miscarriage*, spontaneous abortion, recurrent abortion, spontaneous pregnancy loss, recurrent pregnancy loss, fetal death, vitamin*, folate, folic acid; and also MEDLINE (1966 to May 2003), Current Contents (1998 to May 2003) and EMBASE (1980 to May 2003) using the search strategy given below:

1. miscarriage*
2. spontaneous abortion
3. recurrent abortion
4. habitual abortion
5. spontaneous pregnancy loss
6. recurrent pregnancy loss
7. early pregnancy loss
8. early pregnancy bleeding
9. fetal death
10. #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9
11. vitamin*
12. retinol*
13. carotenoid*
14. thiamin*
15. riboflavin
16. niacin or nicotinamide or nicotinic acid
17. pantothenic acid or pantothenate
18. pyridox*
19. cyanocobalamin or cobalamin
20. ascorb*
21. calciferol
22. tocopherol* or alpha-tocopherol
23. folate*
24. folic acid
25. phylloquinone
26. menaquinone
27. #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25 or #26 or #11 or #12
28. #10 and #27
29. random*
30. controlled-clinical-trial
31. #29 or #30
32. #28 and #31

WHAT'S NEW

Date	Event	Description
6 November 2015	New citation required but conclusions have not changed	Conclusion unchanged.
6 November 2015	New search has been performed	Search updated and 15 new trials included (Bhutta 2009; Hans 2010, Jauniaux 2004; McCance 2010; Prawirohartono 2011; Poston 2006 ;Roberts 2010; Sunawang 2009; Tofail 2008; West 2011; West 2014; Wibowo 2012; Xu 2010; Zagre 2007; Zeng 2008); an additional nine trials have been excluded (Christian 2003; Chelchowska 2004; Correia 1982; Hekmatdoost 2011; Kaestel 2005;

Date	Event	Description
		Potdar 2014; Taylor 1982; Wehby 2012; Young 2015). Three trials are awaiting classification (Adu-Afarwuah 2015; Agarwal 2012a; Prado 2015) and one is ongoing. (Johns 2004). We have revised the outcomes to restrict the scope of the current update to look at miscarriage and miscarriage-related outcomes (Differences between protocol and review). Six new authors joined the team for the 2015/2016 update: Erika Ota, Olukunmi Balogun, Katharina da Silva Lopes, Yo Takemoto, Mizuki Takegata and Rintaro Mori. Three authors who contributed to previous versions of this review stepped down for this update: Ning Pan, Caroline Crowther and Philippa Middleton.

HISTORY

Protocol first published: Issue 1, 2003
Review first published: Issue 2, 2005

Date	Event	Description
27 August 2010	New citation required but conclusions have not changed	Substantive amendment and addition of a new author.
27 August 2010	New search has been performed	Search updated. 11 new studied included (Fawzi 2007; Fleming 1986; Osrin 2005; Roberfroid 2008; Rumbold 2006; Rumiris 2006; Spinnato 2007; Taylor 1982a; Summit 2008; Van den Broek 2006; Villar 2009), 3 studies excluded (Feyi-Waboso 2005; Huybregts 2009; Shu 2002). Two new studies are awaiting classification (Chelchowska 2004b; Kubik 2004b) and two new ongoing trials were identified (Fall 2007b; Johns 2004; Sezikawa 2007).
20 September 2008	Amended	Converted to new review format.

CONTRIBUTIONS OF AUTHORS

Olukunmi Balogun: screened studies for inclusion/exclusion, data extraction, 'Risk of bias' assessment, data analysis, manuscript revision.

Kathrina da Silva Lopes: screened studies for inclusion/exclusion, data extraction, 'Risk of bias' assessment, manuscript revision.

Erika Ota: screened studies for inclusion/exclusion, statistical support, 'Summary of findings' tables, overall supervision.

Yo Takemoto: screened studies for inclusion/exclusion, data extraction, 'Risk of bias' assessment, manuscript revision.

Alice Rumbold: overall supervision.

Mizuki Takegata: data extraction, 'Risk of bias' assessment.

Rintaro Mori: statistical support, overall supervision.

DECLARATIONS OF INTEREST

Alice Rumbold is an investigator on the Australian Collaborative Trial of Supplements with vitamin C and vitamin E for the prevention of pre-eclampsia (Rumbold 2006). This trial is included in this review but its eligibility for inclusion, trial quality assessments and data extraction were carried out independently by two of the review authors not involved in the original trial.

Erika Ota: none known.

Olukunmi O Balogun: none known.

Katharina da Silva Lopes: none known.

Yo Takemoto: none known.

Mizuki Takegata: none known.

Rintaro Mori's institution receives government funding from the Clinical Research Program for Child Health and Development, AMED, Japan to provide support for the PCG Satellite in Japan.

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Internal sources

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External sources

- Japan Agency for Medical Research and Development, Japan.

  The National Research Center for Child Health and Development, Japan receives government funding (AMED No.27300101) from the Clinical Research Program for Child Health and Development, AMED, Japan to support the Cochrane Pregnancy and Childbirth Satellite in Japan

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

2011 update

We now include trials where supplementation occurred in mid-pregnancy. This was not specified in the original protocol for this review, but this was amended to be in line with other miscarriage reviews such as 'Progestogen for preventing miscarriage' (Haas 2009). We included trials where the onset of supplementation occurred both prior to and after 20 weeks' gestation, and when it could not be established whether the majority of the women started supplementation prior to 20 weeks' gestation. To overcome differences in the definition of miscarriage and stillbirth, we have used a combined outcome of total fetal loss (early or late miscarriage or stillbirth). We have still reported early or late miscarriage and stillbirth separately in addition to this combined outcome. Similarly, we specified in the original protocol that we would exclude studies reporting greater than 20% losses to follow-up. In this review we have included studies that reported more than 20% losses to follow-up and undertaken further analyses based on trial quality.

2016 update
The methods section was updated to current Cochrane Pregnancy and Childbirth standard text.

The scope of the current update has been restricted to look at miscarriage and miscarriage-related outcomes. Comparison 1 (any vitamins) and comparison 2 (sensitivity analysis) have been deleted in this update. After discussion it was decided that it did not make sense to compare any vitamin supplementation with no supplementation from either a clinical or consumer perspective.

We deleted the following primary outcomes.
For the woman

1. Placental abruption.
2. Pre-eclampsia.
3. Psychological effects (anxiety and depression) (previously included as maternal outcomes)

For the infant

1. Preterm birth (defined as birth less than 37 weeks' gestation).
2. Birthweight.
3. Small-for-gestational age (birthweight less than the third centile or the most extreme centile reported) (previously included as infant outcomes)

and secondary outcomes:

Secondary outcomes

1. Multiple pregnancy (including only trials supplementing women prior to or around the time of conception).

2. Very preterm birth (defined as less than 34 weeks' gestation).
3. Apgar score less than seven at five minutes.
4. Use of blood transfusion for the mother.
5. Anaemia (maternal and infant).
6. Placental weight.
7. Methods of feeding: breastfeeding, formula or both.
8. Subsequent fertility (subsequent pregnancy rate per couple or as defined by the authors).
9. Poor growth at childhood follow-up.
10. Disability at childhood follow-up.
11. Maternal views of care.
12. Gynaecological hospital admission.
13. Admission to neonatal intensive care unit.
14. Healthcare costs.

All subgroups have been deleted from any analysis.

INDEX TERMS

Medical Subject Headings (MeSH)

Abortion, Habitual [prevention & control]; Abortion, Spontaneous [*prevention & control]; Antioxidants [administration & dosage]; Ascorbic Acid [administration & dosage]; Dietary Supplements [*adverse effects]; Folic Acid [administration & dosage]; Iron [administration & dosage]; Pre-Eclampsia [prevention & control]; Pregnancy Outcome; Pregnancy, Multiple; Prenatal Care; Randomized Controlled Trials as Topic; Stillbirth; Vitamin A [administration & dosage]; Vitamins [*administration & dosage] [adverse effects]

MeSH check words

Female; Humans; Pregnancy